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(54) Title: METHODS AND COMPOSITIONS FOR TREATING INFLAMMATORY DISEASES UTILIZING INHIBITORS OF TUMOR NECROSIS FACTOR ACTIVITY

(57) Abstract

Methods and compositions that act as specific inhibitors of TFN–dependent NF–κB activation signaled by certain members of the TFN receptor superfamily for the prophylaxis and treatment of inflammatory diseases.

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Description

Methods and Compositions for Treating Inflammatory Diseases Utilizing Inhibitors of Tumor Necrosis Factor Activity

Technical Field

The present invention relates to the prophylaxis and treatment of inflammatory diseases and, more particularly, to compounds that act as specific inhibitors of TNF-dependent NF-κB activation signaled by certain members of the TNF receptor superfamily, such as TNF-R1, methods and means for making such inhibitors and their use as pharmaceuticals.

Background of the Invention

Tumor necrosis factors (TNFs), formerly known as lymphotoxins, are cytokines produced mainly by activated macrophages. TNFs originally were identified by their ability to target tumor cells *in vitro* and *in vivo* for growth inhibition and cytolysis. Much of the interest attending the discoveries of these uses was based on their differential cytotoxicity. While TNFs will directly lyse many types of tumor cells, they have generally been considered to be relatively innocuous for normal untransformed, non-virally infected, non-cancerous cells. It has long been know that there are two distinct forms of TNF, tumor necrosis factor-alpha (TNF-α) and tumor necrosis factor-beta (TNF-β). These factors share amino acid sequence identity of 30% and show similarities in many of their biologic functions.

TNFs are now known to elicit a wide range of biological effects, including playing an important role in endotoxic shock and in inflammatory, immunoregulatory, cardiovascular, proliferative, cytotoxic, and anti-viral activities (reviewed by Goeddel *et al.*, CSH Symposia on Quantitative Biology **51**:597-609 (1986)). TNF-α has been said to have a central role in the immune response (Gamble *et al.*, *Proc. Natl. Acad. Sci. USA* **82**:8667 (1985)), but the precise nature of that role remains clouded. It is known that TNF-α plays a multiple role as a mediator of inflammation and the immune response. The level of TNF-α is elevated in pathophysiological conditions, including sepsis syndrome, bacterial meningitis, CHF, cerebral malaria, AIDS, IBD, and RA

(Eigler *et al.*, *Immunol. Today* **18**:487-492 (1997)). Successful use of anti-TNF antibody therapy has recently been reported for patients with rheumatoid arthritis and Crohn's disease (Stack *et al.*, *Lancet* **349**:521-524 (1997)).

Human TNF-α is synthesized as a precursor polypeptide consisting of 233 amino acids and is processed post-translationally to the secretory mature form consisting of the precursor's C-terminal 155 amino acids (Yamada *et al.*, *Biotechnol.* **3**:141-153 (1985)). The three-dimensional structure and functional features of TNF-α and TNF-β have been well characterized by a combination of x-ray crystallography and site directed mutagenesis studies (Zhang *et al.*, *J. Biol. Chem.* **267**:24069-24075 (1992); Van Ostade *et al.*, *Protein Eng.* 7:5-22 (1994); Banner *et al.*, *Cell* **73**:431-445 (1993)). Although TNF-α and TNF-β only share 32% identity in primary sequence, the crystal structures of both TNFs reveals that each monomer consists of two anti-parallel β-pleated sheets with a jelly roll topology and that monomers interact with each other in a head-to-tail fashion to form a homotrimeric structure (Eck *et al.*, *J. Biol. Chem.* **267**:2119-2122 (1992)). In addition, both TNF-α and TNF-β bind to TNF receptors with similar affinities, suggesting that TNF-α and TNF-β bind to the same site on the TNF receptor.

The induction of the various cellular responses mediated by TNF is initiated by its interaction with two distinct cell surface receptors, an approximately 55 kDa receptor termed TNF-R1 and an approximately 75 kDa receptor termed TNF-R2. Human and mouse cDNAs corresponding to both receptor types have been isolated and characterized (Loetscher *et al.*, *Cell* **61**:351 (1990); Schall *et al.*, *Cell* **61**:361 (1990); Smith *et al.*, Science **248**:1019 (1990); Lewis *et al.*, *Proc. Natl. Acad. Sci. USA* **88**:2830-2834 (1991); Goodwin *et al*, *Mol. Cell. Biol.* **11**:3020-3026 (1991)). Both TNF-Rs share the typical structure of cell surface receptors including extracellular, transmembrane and intracellular regions. The extracellular portions of both receptors are found naturally also as soluble TNF-binding proteins (Nophar *et al.*, *EMBO J.* **9**:3269 (1990) and Kohno *et al.*, *Proc. Natl. Acad. Sci. USA* **87**:8331 (1990)). The amino acid sequence of human TNF-R1 and the underlying nucleotide sequence are

disclosed in EP 417,563, whereas EP 418,014 discloses the amino acid and nucleotide sequences of human TNF-R2.

Both TNF receptors are independently active in signaling TNF responses. Direct signaling by TNF-R2 has been observed in lymphoid cells in which TNF-R2 stimulates the proliferation of thymocytes and a murine cytotoxic T cell line CT6 (Tartaglia *et al.*, *Proc. Natl. Acad. Sci. USA* **88**:9292-9296 (1991); Tartaglia *et al.*, *J. Immunol.* **151**:4637-4641 (1993)). Both TNF-R1 and TNF-R2 along with other members of the TNF receptor superfamily, e.g. CD40, have been shown to independently mediate the activation of the transcription factor NF-κB (Lenardo & Baltimore, *Cell* **58**:227-229 (1989); Legreid *et al.*, *J. Biol. Chem.* **269**:7785-7791 (1994); Rothe *et al.*, *Cell* **78**:681-692 (1994); Wiegmann *et al.*, *J. Biol. Chem.* **267**:17997-18001 (1992)). NF-κB is a member of the Rel family of transcriptional activators that control the expression of a variety of important cellular and viral genes (Lenardo & Baltimore, supra, and Thanos and Maniatis, *Cell* **80**:529-532 (1995)). TNF-R2 also mediates the transcriptional induction of the granulocyte-macrophage colony stimulating factor (GM-CSF) gene (Miyatake *et al.*, *EMBO J.* **4**:2561-2568 (1985); Stanley *et al.*, *EMBO J.* **4**:2569-2573 (1985)) and the A20 zinc finger protein gene (Opipari *et al.*, *J. Biol. Chem.* **265**:14705-14708 (1990)) in CT6 cells, and participates as an accessory component to TNF-R1 in the signaling of responses primarily mediated by TNF-R1, like cytotoxicity (Tartaglia and Goeddel, *Immunol. Today* **13**:151-153 (1992)).

The effects of TNF-α are transmitted via membrane bound TNF receptors TNF-R1 (p55) and TNF-R2 (p75) (Banner, *et al.*, *supra* (1993)). While the TNF-α and TNF-R1 complex signals a large number of TNF activities, such as cytotoxicity, manganese superoxide dismutase induction, fibroblast proliferation, and NF-κB induction, the TNF-α and TNF-R2 complex is involved in the proliferation of primary thymocytes and T cells (Schalaby *et al.*, *J. Exp. Med.* **172**:1517-1520 (1990); Tartaglia *et al.*, *Proc. Natl. Acad. Sci USA* **88**:9292-9296 (1991)). Recently, by increasing IκBα level using adenoviral transfer, the nature inhibitor of NF-κB, Foxwell, *et al.*, showed that the spontaneous production of TNF-α from human rheumatoid joint cell cultures

was inhibited by 75% (Foxwell, *et al.*, *Proc. Natl. Acad. Sci USA* **95**:8211-8215 (1998)). This indicated that activation of NF-κB is an essential step for TNF-α synthesis in synovial macrophages and demonstrated that design of a potent and long acting TNF-R1 antagonists to block NF-κB pathway should be sufficient and effective for the treatment of inflammatory diseases, such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD). Other quandaries exist in the arthritis field. For example, research has been directed at drugs that block interleukin-1, presumably in order to suppress immune function, while other workers have suggested administering interleukin-2, despite its immunopotentiating action, because of indications that arthritis patients are deficient in interleukin-2.

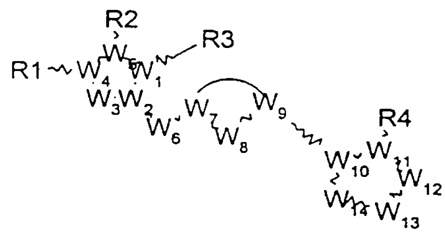
In summary, a variety of tentative and hypothetical postulates exist for the mechanisms underlying various immune-mediated inflammatory responses. Many of the postulates are mutually inconsistent and most are based on observations which cannot distinguish cause from epiphenomenology.

Accordingly, it is an object herein to provide compositions that are capable of precisely targeting acute immune inflammatory responses without producing significant undesirable side effects.

This and other objects will be apparent from consideration of the specification as a whole.

Disclosure of the Invention

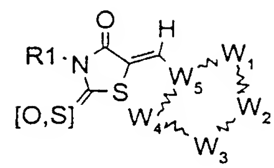
The present invention provides methods, compounds and compositions for treating inflammatory diseases by inhibiting tumor necrosis factor activity. In one aspect, the invention provides a compound of the formula:



wherein

W1W2W3W4W5 is an alicyclic, heterocyclic, or heteroaromatic ring, with the provisos that the ring is not fused with any other ring, and the ring is not a pyrrazole, dihydropyrrazole, or tetrahydropyrrazole derivative; the ring containing W7, W8 and W9 is alicyclic, heterocyclic, aromatic or heteroaromatic; and the W10W11W12W13W14 ring is alicyclic, heterocyclic, or heteroaromatic. In such compounds, the bonds between any two adjacent W atoms can be either single, double or aromatic bonds (valence permitting); W6 is not part of a ring; the W9-W10 bond is not part of a ring; W2, W7, W9, and W10 are each independently either N, C, or C with one substituent group (valence permitting); W1, W4, W5, and W11 are each independently either SOx (where x is 1 or 2), N, C, or C with one substituent group (valence permitting); and W3, W6, W8, W12, W13, and W14 are each independently either O, S, SO, SO_2, N, C, C with one substituent group (either single or double bonded), N one substituent group (single bonded), or PO(OR).

An additional aspect of the invention provides a related group of compounds which have proven particularly beneficial for treating inflammatory diseases by inhibiting tumor necrosis factor activity. Such group comprises compounds of the formula:



wherein

W1W2W3W4W5 is an aliphatic, heterocyclic, or heteroaromatic ring, with the provisos that:

If W1 is CW6R2 or NW7R3, where W6 is CR4R5, CR6, O, S, NR7, SO, SO_2, CO, C=NOR8, or C=NNR9R10, and W7 is CR4R5, CR6, O, NR7, SO, SO_2, CO, C=NOR8, or C=NNR9R10, then W1 is not at a ring bridgehead, and

If R2 and R3 are independently any alicyclic, heterocyclic, aromatic, or heteroaromatic ring structure, then

W2 is O, S, NR11, CR12R13, CR14, SO, or SO_2, (valence permitting),

W3 is O, S, NR15, CR16R17, CR18, SO, or SO_2, (valence permitting),

W4 is O, S, NR19, CR20R21, CR22, SO, or SO_2, (valence permitting),

W5 is N, C, or CR36 (valence permitting)

If W2 is CR23 or NR24 where R23 or R24 is a five membered ring (alicyclic, heterocyclic, or heteroaromatic), then

W1 is O, S, NR25, CR26R27, CR28, SO, or SO_2, (valence permitting),

W3 is O, S, NR29, CR30R31, CR32, SO, or SO_2, (valence permitting),

W4 is O, S, NR33, CR34R35, CR36, SO, or SO_2, (valence permitting),

W5 is N, C, or CR37 (valence permitting),

If the ring W1W2W3W4W5 is neither 3-oxotetrahydrothiophene nor

furan, or if the ring W1W2W3W4W5 is furan and R1 is not any of the groups in Exhibit A, then

W2 can be CR23 or NR24 where R23 or R24 is a six membered ring (alicyclic, heterocyclic, aromatic or heteroaromatic);

in addition,

W1 is O, S, NR25, CR26R27, CR28, SO, or SO_2, (valence permitting),

W3 is O, S, NR29, CR30R31, CR32, SO, or SO_2, (valence permitting),

W4 is O, S, NR33, CR34R35, CR36, SO, or SO_2, (valence permitting),

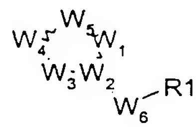
W5 is N, C, or CR37 (valence permitting),

R1 is independently H, heterocyclic, aromatic, heteroaromatic, small alkyl or cycloalkyl, optionally substituted with OH, O-alkyl, S-alkyl, hydroxy alkyl, $CONH_2$, CONH-alkyl, OCF_3, CON-dialkyl, halo, CF_3, sulfonamide, phosphonamide, phosphonate ester, SO-alkyl, SO_2-alkyl, O-aryl, S-aryl, SO-aryl, SO_2-aryl, COO-alkyl, CONH-aryl, acyloxy, acylamino, alkylsulfonylamino, or arylsulfonylamino;

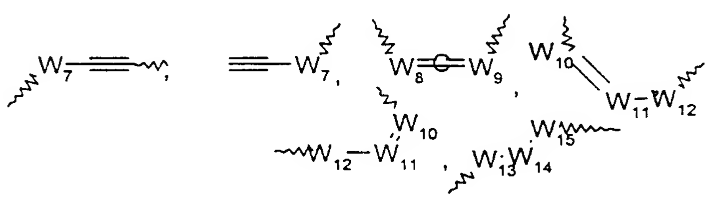
R3, R7 through R11, R15, R19, R24, R25, R29, R33 are each independently, H, heterocyclic, aromatic, heteroaromatic, small alkyl or cycloalkyl, optionally substituted with OH, O-alkyl, S-alkyl, $CONH_2$, CONH-alkyl, CON-dialkyl, F, CF_3, OCF_3, sulfonamide, phosphonamide, or phosphonate ester; and

R2, R4 through R6, R12 through R14, R16 through R18, R20 through R23, R26 through R28, R30 through R32, and R34 through R37 are each independently H, halogen, OH, NH_2, or O-alkyl, OCF_3, O-cycloalkyl, heterocyclic, aromatic, heteroaromatic, small alkyl or cycloalkyl, optionally substituted with OH, O-alkyl, S-alkyl, SO-alkyl, SO_2-alkyl, $CONH_2$, CONH-alkyl, CON-dialkyl, F, CF_3, sulfonamide, phosphonamide, phosphonate ester.

A further aspect of the invention provides a method for treating inflammatory diseases by inhibiting tumor necrosis factor activity comprising administering a compound of the formula:



wherein W1W2W3W4W5 is an alicyclic, heterocyclic or heteroaromatic ring, wherein W1 is O, S, NR2, CHR9, CR10, or P=O(OR43) (valence permitting); W2 is C or N (valence permitting); W3 is C=O, C=S, C-X, CR11, NR12, SO, SO_2, P=O(OR44) (valence permitting); W4 is CR4, NR13, C=S, CO, SO, S, SO_2, P=O(OR45) (valence permitting); W5 is C=O, C=S, C-X, CR3, NR5, SO, SO_2, P=O(OR46) (valence permitting); and W6 is CR47, O, S, SO, SO_2, NR6, CR7R8, P=O(OR48) (valence permitting), or a group of the formula:



where all double bond stereochemistry can independently be either Z or E, and where the bonds from W2 to W6 and from W6 to R1 can be, independently, either single or double (valence permitting). In such compounds, W7 is CR14R15, CO, C=NOR25 or C=NNR26R27; W8 is CR16; W9 is CR17; W10 is N or CR18; W11 is CH, N, CCH_3, CF, CCH_2CH_3, or CCl; W12 is O, S, NR19 or CR20R21; W13 is CR22R23, O, S, NR24, SO_2, SO, CO, C=NOR28, or C=NNR29R30; W14 is CR31R32, O, S, NR33, SO_2, SO, CO, C=NOR34, or C=NNR35R36; W15 is CR37R38, O, S, NR39, SO_2, SO, CO, C=NOR40, or C=NNR41R42; where R1 is any 5- or 6- membered alicyclic,

heterocyclic, aromatic, or heteroaromatic ring, optionally substituted with alkyl, cycloalkyl, branched alkyl, halogen, trifluoroalkyl, alkoxy, aryloxy or benzoyloxy (optionally substituted with nitro, alkyl, branched alkyl or alkoxy), amide, ester, trifluoromethyl, nitro, NR7R8 (where R7 is hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, alkyl, cycloalkyl, heterocylic, alicyclic and R8 is acyl, alkoxyacyl, carbamoyl, N-alkylcarbamoyl, alkoxycarbonyl, hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, alkyl, cycloalkyl, heterocylic, alicyclic), preferably substituted with a 5- or 6-membered ring attached directly or through O, NH, CH_2, S, NCHO, NCH_3, CO, CHOH, $CHCH_3$, or $C=CH_2$; R2, R5, R6, R12, R13, R19, R24 through R30, R33 through R36, R39 through R46, R48 are each independently, H, heterocyclic, aromatic, heteroaromatic, allyl, alkenyl alkyl, alkenyl, small alkyl or cycloalkyl, optionally substituted with OH, O-alkyl, S-alkyl, $CONH_2$, CONH-alkyl, CON-dialkyl, NHCO-alkyl, NHCO-aryl, NHCO-heteroaryl, F, CF_3, sulfonamide, phosphonamide, phosphonate ester; and R3, R4, R7 through R11, R14 through R18, R20 through R23, R31, R32, R37, R38, R47 are each independently H, halogen, OH, NH_2, or O-alkyl, O-cycloalkyl, heterocyclic, aromatic, heteroaromatic, small alkyl or cycloalkyl, optionally substituted with OH, O-alkyl, S-alkyl, SO-alkyl, SO_2-alkyl, $CONH_2$, CONH-alkyl, CON-dialkyl, F, CF_3, OCF_3, sulfonamide, phosphonamide, or phosphonate ester; together with a pharmaceutically acceptable carrier to a patient in need of such treatment.

Such compounds and compositions will be found suitable for use as specific inhibitors of TNF-dependent NF-κB activation signaled by certain members of the TNF receptor superfamily for the prophylaxis and treatment of inflammatory diseases.

Brief Description of the Drawing

Figure 1 graphically depicts structures of a selected group of compounds according to the present invention.

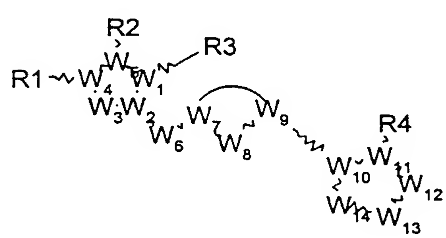
Detailed Description of the Invention

The present invention provides methods, compounds and compositions for treating inflammatory diseases by inhibiting tumor necrosis factor activity.

In the disclosure which follows, the term TNF shall include both tumor necrosis factor-α (TNF-α) and tumor necrosis factor-β (TNF-β), from animals or humans, together with naturally occurring alleles thereof. TNF-α is described by Pennica *et al.*, *Nature* 312:721 (1984). TNF-β is described by Gray *et al.*, *Nature* 312:724 (1984).

The novel compositions for use herein are TNF receptor antagonists. These substances function by competing with native TNF for the cell surface receptor to which TNF binds and blocks the inflammatory events (hereinafter termed competitive antagonists). TNF receptor antagonists are useful, either alone or together with other therapeutic compositions, in the treatment of inflammatory responses.

Thus, in one aspect, the invention provides a compound of the formula:

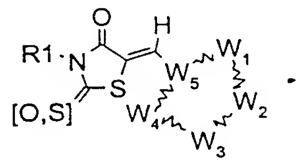


wherein

W1W2W3W4W5 is an alicyclic, heterocyclic, or heteroaromatic ring, with the provisos that the ring is not fused with any other ring, and the ring is not a pyrrazole, dihydropyrrazole, or tetrahydropyrrazole derivative; the ring containing W7, W8 and W9 is alicyclic, heterocyclic, aromatic or heteroaromatic; and the W10W11W12W13W14 ring is alicyclic, heterocyclic, or heteroaromatic. In such compounds, the bonds between any two adjacent W atoms can be either single, double or aromatic bonds (valence permitting); W6 is not part of a ring; the W9-W10 bond is not part of a ring; W2, W7, W9, and W10 are each independently either N, C, or C with one substituent group (valence permitting); W1, W4, W5, and W11 are each

independently either SOx (where x is 1 or 2), N, C, or C with one substituent group (valence permitting); and W3, W6, W8, W12, W13, and W14 are each independently either O, S, SO, SO_2, N, C, C with one substituent group (either single or double bonded), N one substituent group (single bonded), or PO(OR).

In addition, the invention provides a related group of compounds which have proven particularly beneficial for treating inflammatory diseases by inhibiting tumor necrosis factor activity. Such group comprises compounds of the formula:



wherein

W1W2W3W4W5 is an aliphatic, heterocyclic, or heteroaromatic ring, with the provisos that:

If W1 is CW6R2 or NW7R3, where W6 is CR4R5, CR6, O, S, NR7, SO, SO_2, CO, C=NOR8, or C=NNR9R10, and W7 is CR4R5, CR6, O, NR7, SO, SO_2, CO, C=NOR8, or C=NNR9R10, then W1 is not at a ring bridgehead, and

If R2 and R3 are independently any alicyclic, heterocyclic, aromatic, or heteroaromatic ring structure, then

W2 is O, S, NR11, CR12R13, CR14, SO, or SO_2, (valence permitting),

W3 is O, S, NR15, CR16R17, CR18, SO, or SO_2, (valence permitting),

W4 is O, S, NR19, CR20R21, CR22, SO, or SO_2, (valence permitting),

W5 is N, C, or CR36 (valence permitting)

If W2 is CR23 or NR24 where R23 or R24 is a five membered ring

(alicyclic, heterocyclic, or heteroaromatic), then

W1 is O, S, NR25, CR26R27, CR28, SO, or SO_2, (valence permitting),

W3 is O, S, NR29, CR30R31, CR32, SO, or SO_2, (valence permitting),

W4 is O, S, NR33, CR34R35, CR36, SO, or SO_2, (valence permitting),

W5 is N, C, or CR37 (valence permitting),

If the ring W1W2W3W4W5 is neither 3-oxotetrahydrothiophene nor furan, or if the ring W1W2W3W4W5 is furan and R1 is not any of the groups in Exhibit A, then

W2 can be CR23 or NR24 where R23 or R24 is a six membered ring (alicyclic, heterocyclic, aromatic or heteroaromatic);

in addition,

W1 is O, S, NR25, CR26R27, CR28, SO, or SO_2, (valence permitting),

W3 is O, S, NR29, CR30R31, CR32, SO, or SO_2, (valence permitting),

W4 is O, S, NR33, CR34R35, CR36, SO, or SO_2, (valence permitting),

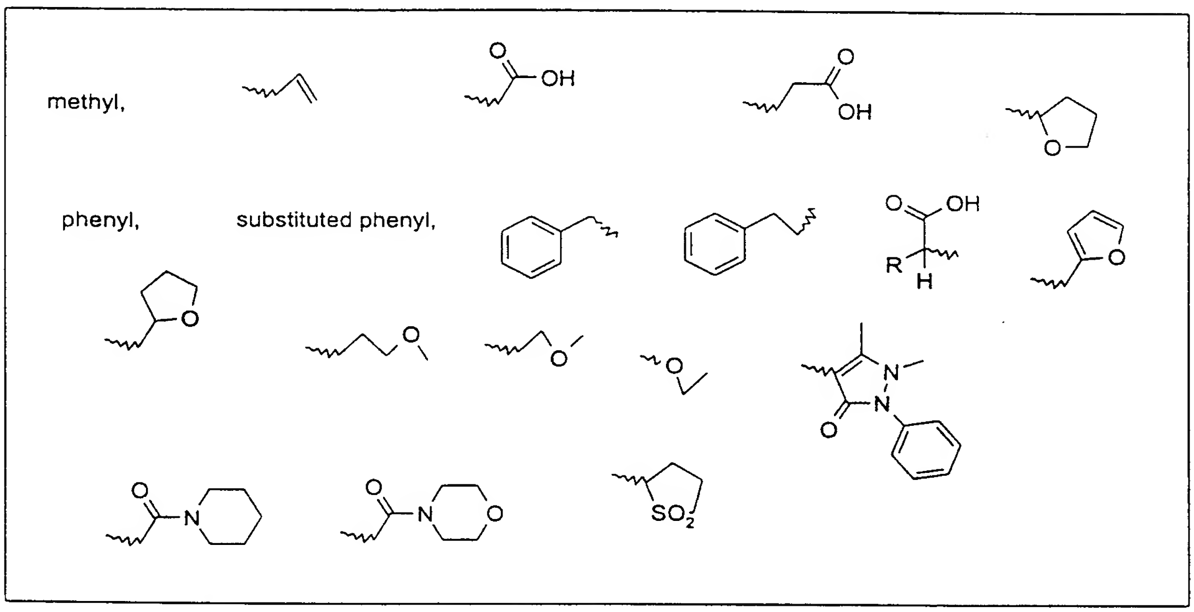
W5 is N, C, or CR37 (valence permitting),

R1 is independently H, heterocyclic, aromatic, heteroaromatic, small alkyl or cycloalkyl, optionally substituted with OH, O-alkyl, S-alkyl, hydroxy alkyl, $CONH_2$, CONH-alkyl, OCF_3, CON-dialkyl, halo, CF_3, sulfonamide, phosphonamide, phosphonate ester, SO-alkyl, SO_2-alkyl, O-aryl, S-aryl, SO-aryl, SO_2-aryl, COO-alkyl, CONH-aryl, acyloxy, acylamino, alkylsulfonylamino, or arylsulfonylamino;

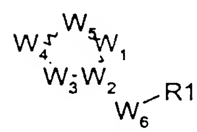
R3, R7 through R11, R15, R19, R24, R25, R29, R33 are each independently, H, heterocyclic, aromatic, heteroaromatic, small alkyl or cycloalkyl, optionally substituted with OH, O-alkyl, S-alkyl, $CONH_2$, CONH-alkyl, CON-dialkyl, F, CF_3, OCF_3, sulfonamide, phosphonamide, or phosphonate ester; and

R2, R4 through R6, R12 thorugh R14, R16 through R18, R20 through R23, R26 through R28, R30 through R32, and R34 through R37 are each independently H, halogen, OH, NH_2, or O-alkyl, OCF_3, O-cycloalkyl, heterocyclic, aromatic, heteroaromatic, small alkyl or cycloalkyl, optionally substituted with OH, O-alkyl, S-alkyl, SO-alkyl, SO_2-alkyl, $CONH_2$, CONH-alkyl, CON-dialkyl, F, CF_3, sulfonamide, phosphonamide, phosphonate ester.

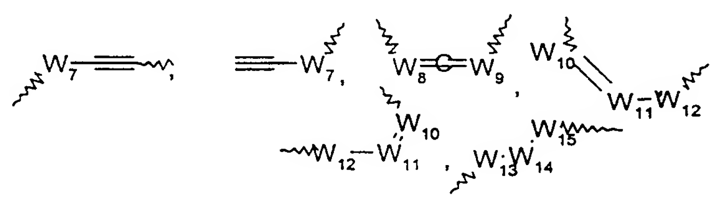
Exhibit A



An additional aspect of the invention provides a method for treating inflammatory diseases by inhibiting tumor necrosis factor activity comprising administering a compound of the formula:



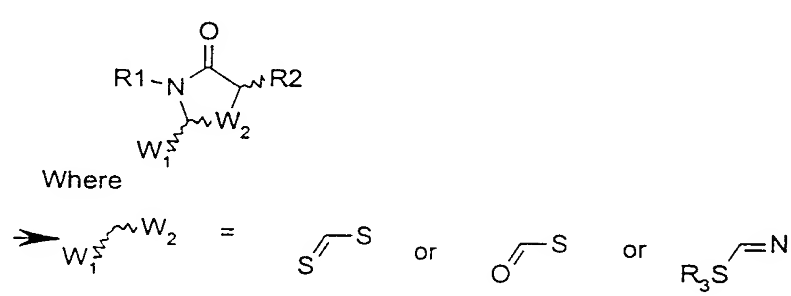
wherein W1W2W3W4W5 is an alicyclic, heterocyclic or heteroaromatic ring, wherein W1 is O, S, NR2, CHR9, CR10, or P=O(OR43) (valence permitting); W2 is C or N (valence permitting); W3 is C=O, C=S, C-X, CR11, NR12, SO, SO_2, P=O(OR44) (valence permitting); W4 is CR4, NR13, C=S, CO, SO, S, SO_2, P=O(OR45) (valence permitting); W5 is C=O, C=S, C-X, CR3, NR5, SO, SO_2, P=O(OR46) (valence permitting); and W6 is CR47, O, S, SO, SO_2, NR6, CR7R8, P=O(OR48) (valence permitting), or a group of the formula:



where all double bond stereochemistry can independently be either Z or E, and where the bonds from W2 to W6 and from W6 to R1 can be, independently, either single or double (valence permitting). In such compounds, W7 is CR14R15, CO, C=NOR25 or C=NNR26R27; W8 is CR16; W9 is CR17; W10 is N or CR18; W11 is CH, N, CCH_3, CF, CCH_2CH_3, or CCl; W12 is O, S, NR19 or CR20R21; W13 is CR22R23, O, S, NR24, SO_2, SO, CO, C=NOR28, or C=NNR29R30; W14 is CR31R32, O, S, NR33, SO_2, SO, CO, C=NOR34, or C=NNR35R36; W15 is CR37R38, O, S, NR39, SO_2, SO, CO, C=NOR40, or C=NNR41R42; where R1 is any 5- or 6- membered alicyclic,

heterocyclic, aromatic, or heteroaromatic ring, optionally substituted with alkyl, cycloalkyl, branched alkyl, halogen, trifluoroalkyl, alkoxy, aryloxy or benzoyloxy (optionally substituted with nitro, alkyl, branched alkyl or alkoxy), amide, ester, trifluoromethyl, nitro, NR7R8 (where R7 is hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, alkyl, cycloalkyl, heterocylic, alicyclic and R8 is acyl, alkoxyacyl, carbamoyl, N-alkylcarbamoyl, alkoxycarbonyl, hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, alkyl, cycloalkyl, heterocylic, alicyclic), preferably substituted with a 5- or 6-membered ring attached directly or through O, NH, CH_2, S, NCHO, NCH_3, CO, CHOH, $CHCH_3$, or $C=CH_2$; R2, R5, R6, R12, R13, R19, R24 through R30, R33 through R36, R39 through R46, R48 are each independently, H, heterocyclic, aromatic, heteroaromatic, allyl, alkenyl alkyl, alkenyl, small alkyl or cycloalkyl, optionally substituted with OH, O-alkyl, S-alkyl, $CONH_2$, CONH-alkyl, CON-dialkyl, NHCO-alkyl, NHCO-aryl, NHCO-heteroaryl, F, CF_3, sulfonamide, phosphonamide, phosphonate ester; and R3, R4, R7 through R11, R14 through R18, R20 through R23, R31, R32, R37, R38, R47 are each independently H, halogen, OH, NH_2, or O-alkyl, O-cycloalkyl, heterocyclic, aromatic, heteroaromatic, small alkyl or cycloalkyl, optionally substituted with OH, O-alkyl, S-alkyl, SO-alkyl, SO_2-alkyl, $CONH_2$, CONH-alkyl, CON-dialkyl, F, CF_3, OCF_3, sulfonamide, phosphonamide, or phosphonate ester; together with a pharmaceutically acceptable carrier to a patient in need of such treatment.

In addition, an alternative group of related compounds will also find use in the present method for treating inflammatory diseases by inhibiting tumor necrosis factor activity. This group of inhibitors includes compounds of the formula:

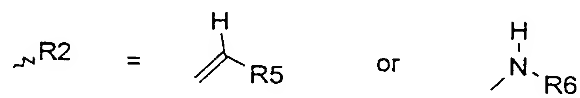


where R3 is H or short alkyl or cycloalkyl;

and wherein

R1 is H, or straight or branched alkyl (C1-C10) optionally substituted by:

COOR4 (where R4 is H, short alkyl, cycloalkyl, branched alkyl), an aromatic or heteroaromatic ring, or by aryloxy; or alkenyl, especially 2-propenyl; or aromatic or heteroaromatic ring-especially furan, optionally substituted by alkyl, hydroxy or alkoxy;



(the bond from 5 membered ring to R2 is double for CHR5 and single for NHR6);

R5 is CR7=CHR8 with R7=H or small alkyl and R8=aryl or heteroaryl, optionally substituted by alkoxy; or aromatic or heteroaromatic (especially phenyl, furyl, thiophenyl, pyrrolyl, thiazolyl) optionally substituted by short alkyl; or nitro; or alkoxy (including multiple alkoxy); or aryloxy optionally substituted by alkoxy or alkyl; or aromatic or heteroaromatic (especially thiophenyl) optionally substituted by halo, trifluoromethyl, trifluoromethoxy, alkoxy, alkyl, COOR10 (where R10 is H, short alkyl, cycloalkyl, branched alkyl) or optionally fused to a 5 membered carboxyclic or heterocyclic ring;

R6 is aromatic or heteroaromatic (especially phenyl, furyl, thiophenyl, pyrrolyl, thiazolyl) optionally substituted by short alkyl; nitro; alkoxy (including multiple alkoxy); aryloxy optionally substituted by alkoxy or alkyl; aromatic or heteroaromatic (especially thiophenyl) optionally substituted by halo, trifluoromethyl, trifluoromethoxy, alkoxy, alkyl, COOR11 (where R11 is H, short alkyl, cycloalkyl, branched alkyl) or optionally fused to a 5 membered carboxyclic or heterocyclic ring; together with a pharmaceutically acceptable carrier to a patient in need of such treatment.

In general, the present inhibitor compounds will be recognized as bearing a structural relationship to thiazolidinedione and 2-thiazolidinedione compounds, although a wide variation of the atomic components of the structures will be expected to preserve the TNF receptor antagonist activity.

Synthesis of Inhibitor Compounds of the Invention

In general, the compounds of the present invention can be prepared in accordance with chemical synthetic protocols well known to those of skill in this art. One desirable category of such techniques is know by the generic term "combinatorial chemistry." Such techniques are well know in the art, and can be generally summarized as follows: For example, preparation of libraries can be by the "split synthesis" method, as described in Gallop *et al.*, *J. Med. Chem.*, 37:1233-1251 (1994). The split synthesis procedure involves dividing a resin support into n equal fractions, in a separate reaction carry out a single reaction to each aliquot, and then thoroughly mixing all the resin particles together. Repeating the protocol for a total of x cycles can produce a stochastic collection of up to n^x different compounds. An alternative format is by preparing sublibraries in the $O_3O_2X_1$ format, wherein two positions on the compounds, O_3 and O_2 are explicitly defined and a third position, X_1, varies. Such sublibraries can be conveniently prepared by the tea-bag technique, as is known in the art, and described, for example in U.S. Pat. No. 4,631,211 and Houghten *et al.*, *Proc. Natl. Acad. Sci.*, 82:5131-5135 (1985).

Alternatively, or in addition thereto, the iterative selection and enhancement process of screening and sublibrary resynthesis can be employed. For example, a sublibrary of various R1 substituents can be screened to select the most active R1 substituent. The compound having the most active R1 is then resynthesized and with the R1 position being defined, a new R2 position mixture library is prepared, screened, and the most active R2 selected. The above process can then be repeated to identify R3 and the other most active R substituents on the W1W2W3W4W5 ring.

In yet another approach, the positional scanning technique, only a single position is defined in a given sublibrary and the most preferred substituent at each position of the compound is identified.

The advantage of synthetic combinatorial libraries (SCLs) made up of mixtures of tens of millions of different compounds is that they can be used to rapidly identify individual, active compounds without the need to individually synthesize, purify, and test every single compound. Since the libraries are in solution (i.e., not attached to a

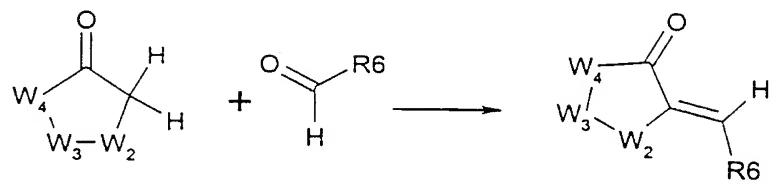
bead, pin, phage, glass, etc.) they can be screened in virtually any assay system.

Solution phase combinatorial chemistry methods can be used when the product can be separated from side products and starting materials through rapid techniques. Examples of these are: (1) selective precipitation of product and removal of byproducts and precursors by washing, (2) selective removal of side products and starting materials using chemically reactive polymers and/or ion exchange polymers ("scavenge"), (3) selective binding of product to a chemically reactive polymer, followed by removal of the product through a second chemical reaction ("capture") (4) selective binding of product to an ion exchange polymer, followed by removal with acid, base, or high salt buffer ("capture"), and (5) selective solubilization of product. Solution phase combinatorial chemistry approaches are covered in a recent set of reviews (*Tetrahedron*, 54:3955-4150 (1998)).

The synthetic approaches described in examples 1-20 can be optimally carried out using solution phase combinatorial chemistry. Several reactions are carried out simultaneously using a multiple reaction vessel block such as, but not limited to, the Charybdis Calypso™ temperature controlled blocks, with gas manifolds to maintain an argon or nitrogen atmosphere. Alternately, the reactions can be carried out simultaneously in multiple vials filled with argon or nitrogen and fitted with magnetic stirbars and polytetrafluoroethylene-lined, sealed caps, by heating and stirring them simultaneously in a magnetic stirrer/heater such as, but not limited to, the Pierce ReactTherm™ III Heating/Stirring Module. The products are isolated by addition of water and filtration using a system such as, but not limited to, the Charybdis Calypso™ filtration block or polypropylene syringes fitted with filter disks made from polyethylene, polytetrafluoroethylene, or glass and attached to a vacuum manifold.

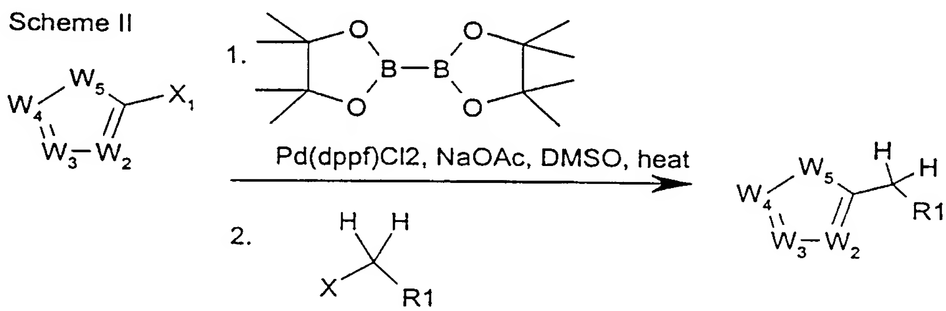
By way of illustration of basic techniques for the synthesis of compounds within the scope of the present invention, schemes I-VII as illustrated below will prove exemplary of such synthetic techniques.

Scheme I

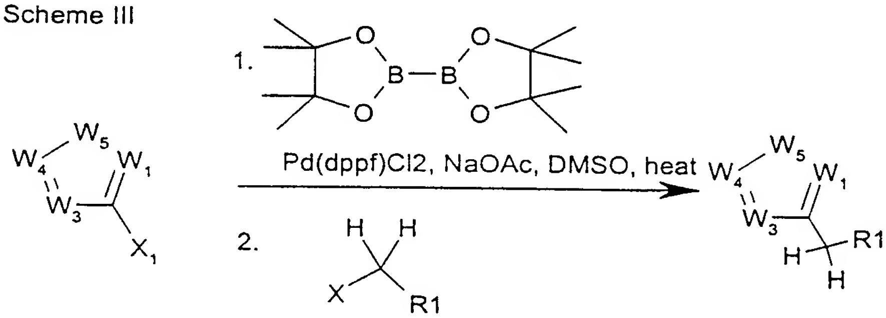


According to reaction scheme I, a heterocycle containing a chemically reactive methylene group in an inert solvent such as dimethylacetamide is treated with an appropriately-substituted aldehyde in the presence of a catalyst such as acetic acid plus sodium acetate, piperidine, or ammonium hydroxide. R1 is any alkyl or aryl group, R2 and R3 are O or no group, (for W4 and W5, see "broadly defined claim for TNF-active compounds", valence permitting).

Scheme II

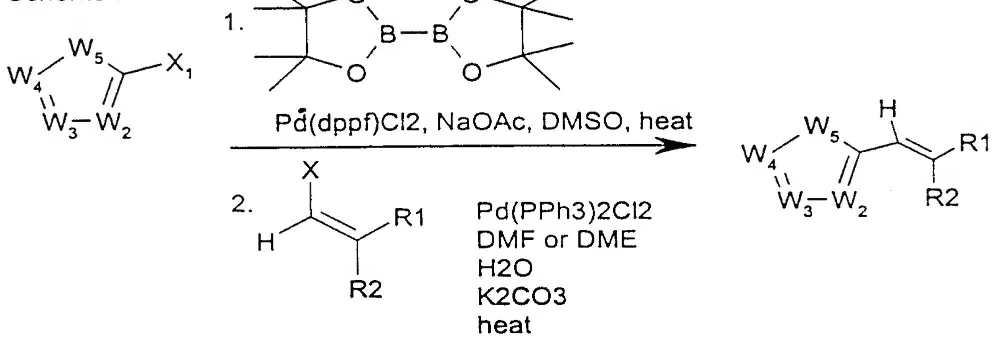


Scheme III

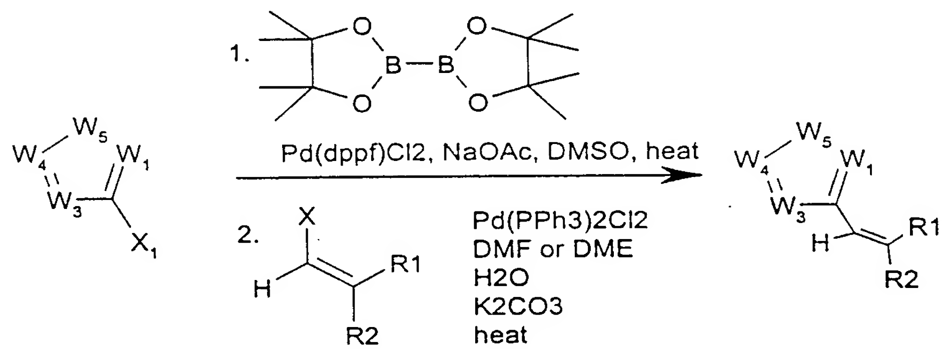


According to either of reaction schemes II and III, a 5-membered ring aromatic halide (X1=Br or I) is converted to the corresponding boronic pinacolate ester in an inert solvent such as DMSO or DMF, and then coupled to a benzylic or allylic halide $R1CH_2X$ (R1=vinyl or aromatic, X=Cl or Br) using a palladium complex. In this illustration, dppf is taken to mean 1,1'bis(diphenylphosphino)ferrocene, and W1-W5, is as previously defined.

Scheme IV

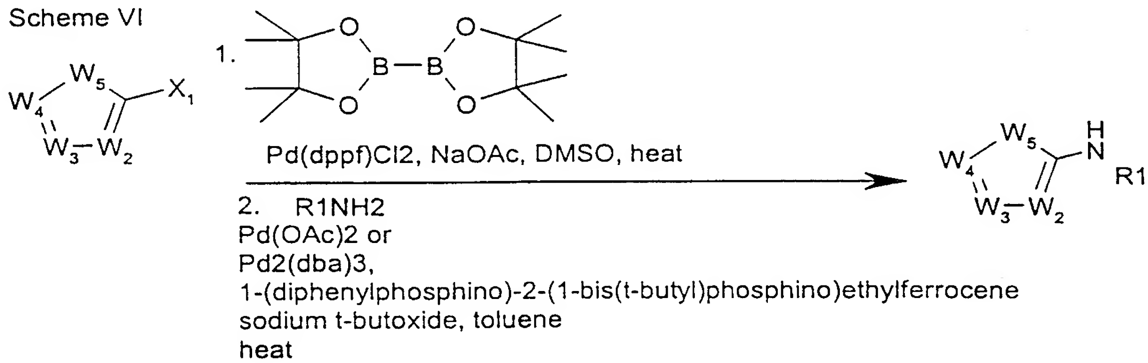


Scheme V

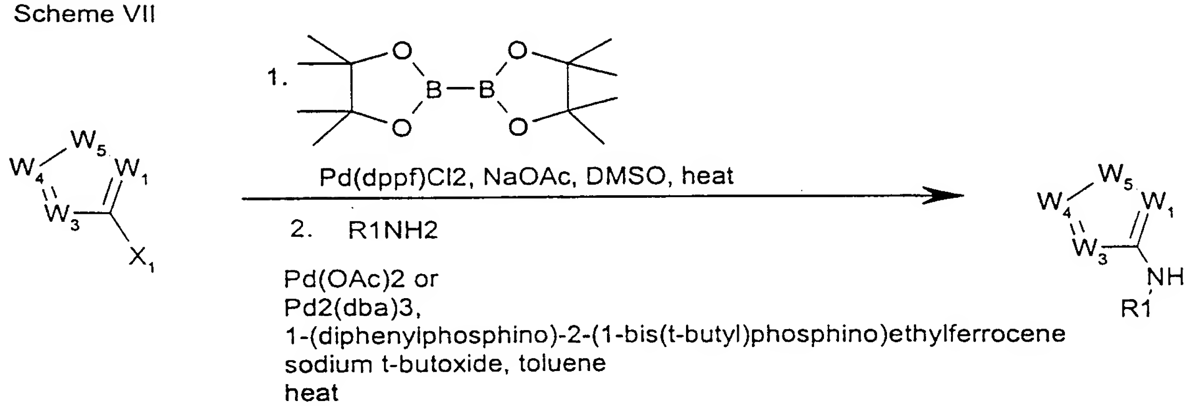


According to either of reaction schemes IV and V, a 5-membered ring aromatic halide (X1 = Br or I) is converted to the corresponding boronic pinacolate ester in an inert solvent such as DMSO or DMF, and then coupled to a vinyl halide R1R2C=CHX (R1 and R2 are aromatic or aliphatic, X is Br or I, and dppf and W1-W5 are as previously defined) using a palladium complex.

Scheme VI



Scheme VII



According to either of reaction schemes VI and VII, a 5-membered ring aromatic halide (X1 is Br or I) is converted to the corresponding boronic pinacolate ester in an inert solvent such as DMSO or DMF, and then coupled to a monoalkyamine or monoarylamine ($R1NH_2$) in toluene (dppf and W1-W5 are as previously defined).

Identification of Potential TNF Receptor Antagonists

Thee are numerous assays available to routinely identify compounds which display activity as TNF receptor antagonists. One assay technique which has been found particularly useful is the Eu^{3+} labeling of TNF-α using a Eu^{3+}-chelate of DTTA, which has demonstrated specific binding to TNF-R1. Eu-labeling reagents are commercially available to link the Eu-chelate covalently to either a free amino group or a sulfhydryl group on the protein. On the basis of the x-ray structure of human TNF-α, six lysines are exposed on the protein surface, whereas two cysteine residues form an intra-disulfide bond, which leaves no free-cysteine accessible for chemical modification. TNF-α, TNF-β, and anti-human TNF-R1 antibodies are able to compete with Eu^{3+}-labeled TNF-α for binding to the receptor. In this manner, highly sensitive, non-radioactive probes are found very useful for high throughput screening of potential small molecule TNF-R1 antagonists.

The screening assay is performed generally as follows:

Eu^{3+}-chelate of N^1-(p-isothiocyanatobenzyl)-diethylenetriamine-N^1, N^2, N^3, N^3-tetraacetic acid (DTTA; Wallac, Gathersburg, MD) is used to prepare [Eu^{3+}]TNF-α. 100μg lyophilized TNF-α is resuspended in 100μL of labeling buffer (50mM $NaHCO_3$, pH 8.5, containing 0.9% NaCl). [Eu^{3+}]-DTTA (50 μg) is then added to TNF-α in the labeling buffer. The reaction is carried out at 4°C for 48 hours. The sample is then diluted 2-fold into 50mM Tris buffer (pH 7.8) containing 0.9% NaCl and 0.05% NaN_3, and dialyzed against 1 liter 50mM Tris buffer to remove free Eu^{3+}-DTTA label. The protein concentration is determined by the Bradford method (Bradford, 1976) and the specific activity is calculated using a europium standard solution (Wallac).

The ligand binding assay is performed as follows: 96-well plates are coated with 10ng of TNF receptor in 50mM $NaHCO_3$ (pH 9.6) overnight at 4°C. Plates are then blocked with 0.2% BSA in PBS buffer, washed once with binding buffer (0.2%BSA/PBS/0.1% Tween-20), and incubated with Eu^{3+}-labeled TNF-α and the test compound for one and a half-hours at room temperature. The plates are then washed three times with DELFIA Wash Solution (Wallac) and 100μl of DELFIA Enhancement Solution (Wallace) is added. The plate is placed on a plate shaker for 10 min before

reading using a Victor Flurometer 1420 (Wallac). The europium counting protocol is used with a 320nm excitation pulse at a frequency of 1000 s^{-1} and detection at 615nm (emission wavelength). Fluorescence signal is measured after a delay of 400 μsec between each excitation pulse. Non-specific binding is defined using TNF-α with 500-fold excess of [Eu^{3+}]TNF-α. Each experimental point is carried out in duplicate.

The data ligand receptor interaction data is analyzed using Prizm (GraphPad Software). Ligand binding data are analyzed by non-linear least-square regression. Saturation data are fitted to a rectangular hyperbola model and competition data are fitted to a sigmoidal curve with a variable slope. Inhibition constants (Ki) are determined from IC_{50}'s using the Chang-Prusoff equation (Cheng, Y.C. and W.H. Prusoff, *Biochem. Pharmacol.* **22**:3099-3108 (1973)).

In addition to showing specific, saturable binding, [Eu^{3+}]-TNF-α could be competed by unlabeled TNF-α and TNF-β with expected potencies. Thus, TNF-α and TNF-β have been shown to identify the same binding sites and present the same pharmacological properties. This results are in agreement with published x-ray structures of TNF-β-TNF-R1 complex and TNF-α (Eck, M.J. and S.R. Sprang, *J. Biol. Chem.* **264**:17595-17605 (1989); Banner, *et al.*, *Cell* **73**:431-445 (1993)). In addition, [Eu^{3+}]TNF-α could be displaced by an anti-human TNF-R1 neutralizing monoclonal antibody, as well as unlabeled TNF-α and TNF-β, suggesting that this antibody neutralizes TNF-R1-mediated bioactivities by blocking TNF-α or TNF-β binding to TNF-R1.

Determination of TNF Receptor Antagonist Biological Activity

Having screened prospective compounds for potential TNF receptor antagonist properties, it is considered desirable to verify the activity in a biological activity assay. TNF-α is know to cause rapid degradation of IκBα, with a concomitant translocation of NF-κB from the cytoplasm to the nucleus in MRC-5 cells (a human embryonal lung cell line (ATCC CCL-171)).

In order to perform such an assay, MRC-5 cells (available as noted above) are incubated at a density of $5x10^4$ cells per chamber in culture medium (Eagle's MEM with 2mM L-glutamine and Earle's BSS adjusted to contain 1.5g/L sodium bicarbonate, 0.1mM non-essential amino acid, 1.0mM sodium pyruvate, 10% fetal bovine serum (FBS)) on Fisher culture slides overnight at 37°C and 5% CO_2.

The next day, the medium is removed and Earle's MEM without FBS is added to each chamber. 0.1nM TNF-α is then added to each as well as 100μM of the test compound (negative control is no TNF-α, positive control is 0.1nM TNF-α with no test compound added). The slides are placed in a 37°C incubator for 15 minutes.

The chambers are washed twice with PBS. The cells are fixed by incubating in ice cold methanol for five minutes and allowed to air dry. The cells are then washed three times with PBS. The specimen is incubated with 10% FBS in PBS for 20 minutes to suppress non-specific binding of IgG, then washed once with PBS.

The chambers are then incubated with goat anti-human NF-κB p65 (Santa Cruz Biotechnology, Inc.) at 1:500 dilution in PBS with 1.5% FBS for 60 minutes. The chambers are then washed three times with PBS for 5 minutes each, and incubated for 45 minutes in a dark chamber with fluorescein goat anti-rabbit IgG (Santa Cruz Biotechnology, Inc.) diluted 1:200 in PBS with 1.5% FBS. After a final wash three times with PBS, a coverslip is mounted with SlowFade™ AntiFade (Molecular Probes).

In order to score the results, the chambers are examined using a fluorescence microscope with an appropriate filter. At least 500 cells are counted per chamber and the location of the fluorescence is noted as either nuclear only, nuclear and cytoplasmic, or cytoplasmic only.

Treatment of Inflammatory Responses

Inflammatory or immune-potentiated inflammatory events to be treated with the present TNF receptor antagonists are characterized by the presence of a humoral and/or cellular response directed against an undesired foreign or self target tissue or by uncertain etiology. Typically, immune potentiating inflammatory events are characterized by antibodies directed against host tissue by way of an aberrant host response, host antibodies against grafted tissue, or antibodies of graft origin directed against host tissue. Such events also are characterized by infiltration of polymorphonuclear neutrophils and mononuclear leukocytes into the target tissue, and subsequent induction of pain, localized edema, possible vascular endothelial injury and excessive production of cytokines by stimulated cells. Other than in transplantation immunity, such events occur during the course of diseases including arthritis, systemic lupus, Crohn's disease, inflammatory bowel disease, and other autoimmune disorders known to those skilled in the art.

The therapeutically effective amounts of the present TNF receptor antagonist will be a function of many variables, including the affinity of the antagonist for the TNF receptor, any residual cytotoxic activity exhibited by competitive antagonists, the route of administration, the clinical condition of the patient (including the desirability of maintaining a non-toxic level of endogenous TNF activity), and whether the receptor antagonist is to be used for the prophylaxis or for the treatment of acute response episodes. Since the maximum tolerated dose of TNF-α in human clinical trials has ranged up to about 25μg per 24 hrs, the molar dose of TNF receptor antagonist will be expected to vary about from 0.001 to 10 times the maximum tolerated molar dose of TNF-α, although as noted above this range will be subject to a great deal of therapeutic discretion. It is to be expected that concentrations of TNF localized at the sites of inflammation may exceed the whole body maximum therapeutic dose. Assay of the TNF concentration in inflammatory infiltrates will provide guidance as to the amount of TNF receptor antagonist to be employed, particularly if localized administration is practical, e.g. in Crohn's disease (suppositories) or arthritis (injections into synovial fluid). Similar dosages and considerations apply in the case of TNF-β. The key factor

in selecting an appropriate dose is the result obtained: If the patient's inflammatory response does not at least partially resolve within about 48 hours after administration, the dose should be gradually elevated until the desired effect is achieved. Also, relatively higher doses will be initially needed for the treatment for acute rejection or inflammatory episodes, i.e., for patients in acute organ transplant rejection or undergoing arthritic flares.

In practicing the method of the present invention, the therapeutic preparation will be administered to a patient in need of anti-inflammatory treatment at a therapeutically effective dosage level. The lowest effective dosage levels can be determined routinely by initiating treatment at higher dosage levels and reducing the dosage level until relief from inflammatory reaction is no longer obtained. Generally, therapeutic dosage levels will range from about 0.01-100μg/kg of host body weight.

The present TNF receptor antagonist can also administered in conjunction with other anti-inflammatory agents used in or proposed for the treatment of individual immunoinflammatory conditions as appropriate, e.g. gold salts, cyclosporin antibiotics, salicylate and corticosteroids (such as methylprednisolone). However, when employed together with TNF receptor antagonists these agents may be employed in lesser dosages than when used alone.

Where combinations are contemplated, it is not intended that the present invention be limited by the particular nature of the combination. The present invention contemplates combinations as simple mixtures as well as chemical hybrids. One example of the latter is where the present compound is covalently linked to a pharmaceutical such as a corticosteroid, or where two or more compounds are joined. For example, covalent binding of the distinct chemical moieties can be accomplished by any one of many commercially available cross-linking compounds.

In view of the therapeutic urgency attendant acute rejection episodes, the TNF receptor antagonist should be intravenously infused or introduced at the inflammatory lesion immediately upon the development of symptoms or serological evidence of TNF activity. However, prophylaxis is suitably accomplished by intramuscular or subcutaneous administration. In this regard, the compositions are prepared as

injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection may also be prepared. These therapeutic preparations can be administered to mammals for veterinary use, such as with domestic animals, and clinical use in humans in a manner similar to other therapeutic agents. In general, the dosage required for therapeutic efficacy will vary according to the type of use and mode of administration, as well as the particularized requirements of individual hosts.

It is not intended that the present invention be limited by the particular nature of the therapeutic preparation. For example, such compositions can be provided together with physiologically tolerable liquid, gel or solid carriers, diluents, adjuvants and excipients. Such compositions are typically prepared as sprays (e.g. intranasal aerosols) for topical use. However, they may also be prepared either as liquid solutions or suspensions, or in solid forms including respirable and nonrespirable dry powders. Oral formulations (e.g. for gastrointestinal inflammation) usually include such normally employed additives such as binders, fillers, carriers, preservatives, stabilizing agents, emulsifiers, buffers and excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, magnesium carbonate, and the like. These compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations, or powders, and typically contain 1%-95% of active ingredient, preferably 2%-70%.

The compounds of the present invention are often mixed with diluents or excipients which are physiologically tolerable and compatible. Suitable diluents and excipients are, for example, water, saline, dextrose, glycerol, or the like, and combinations thereof. In addition, if desired the compositions may contain minor amounts of auxiliary substances such as wetting or emulsifying agents, stabilizing or pH buffering agents.

Additional formulations which are suitable for other modes of administration, such as topical administration, include salves, tinctures, creams, lotions, and, in some cases, suppositories. For salves and creams, traditional binders, carriers and excipients may include, for example, polyalkylene glycols or triglycerides.

The following examples serve to illustrate certain preferred embodiments and aspects of the present invention and are not to be construed as limiting the scope thereof.

Experimental

In the experimental disclosure which follows, all weights are given in grams (g), milligrams (mg), micrograms (μg), nanograms (ng), or picograms (pg), all amounts are given in moles, millimoles (mmol), micromoles (μmol), nanomoles (nmol), picomoles (pmol), or femtomoles (fmol), all concentrations are given as percent by volume (%), proportion by volume (v:v), molar (M), millimolar (mM), micromolar (μM), nanomolar (nM), picomolar (pM), femtomolar (fM), or normal (N), all volumes are given in liters (L), milliliters (mL), or microliters (μL), and linear measurements are given in millimeters (mm), or nanometers (nm) unless otherwise indicated.

The following examples demonstrate the practice of the present invention in synthesizing compounds according to the invention, generally as depicted in Figure 1, and in methods by which drugs having the formulas shown can be readily identified by routine assay procedures to demonstrate that they possess the desired activity:

Example 1

E-5-(5-methylfuran-2-ylmethylene)-2-thioxo-3-methyl-thiazolidin-4-one

5-Methylfuran-2-carboxaldehyde (70.4mg, 0.64mmol) and 2-thioxo-3-methyl-thiazolidin-4-one (94.2mg, 0.64mmol) are stirred in 0.32mL dimethylacetamide and 0.32mL acetic acid containing sodium acetate (26mg, 0.32mmol) for 67 hours at 85°C under an argon or nitrogen atmosphere. Cold water (7mL, 5°C) is added to the reaction mixture, resulting in a precipitate. After filtration and washing with 15mL cold water, the residue is dissolved in 24mL of 9:1 methylene chloride, filtered and stripped of solvent under high vacuum yielding 87mg of the title compound (56% yield).

^{1}HNMR (500MHz, $CDCl_3$):

δ: 7.41 1Hs, 6.77 1Hd (J=3.3), 6.21 1Hd (J=3.3), 3.50 3Hs, 2.42 3Hs

Example 2

E-5-(5-methylfuran-2-ylmethylene)-2-thioxo-3-allyl-thiazolidin-4-one

5-Methylfuran-2-carboxaldehyde and 2-thioxo-3-allyl-thiazolidin-4-one are converted to the title compound generally according to the protocol of Example 1.

^{1}HNMR (500MHz, DMSO-d_6):

δ: 7.6 1Hs, 7.18 1Hd (J=3.3Hz), 6.47 1Hd (J=3.6 Hz), 5.84 1Hm, 5.17 1Hd (J=11.3 Hz), 5.11 1Hd (J=18.3 Hz), 4.63 2Hd (J=4.9 Hz), 2.43 3Hs.

Example 3

E-5-(thiazol-2-ylmethylene)-2-thioxo-3-allyl-thiazolidin-4-one

Thiazol-2-carboxaldehyde and 2-thioxo-3-allyl-thiazolidin-4-one are converted to the title compound generally according to the protocol of Example 1.

^{1}HNMR (500MHz, DMSO-d_6):

δ: 8.24 1Hd (J=3.0Hz), 8.11 1Hd (J=3.3 Hz), 8.09 1Hs, 5.85 1Hm, 5.18 1Hm, 5.13 1Hd (J=16.5Hz), 4.64 2Hd (J=4.9).

Example 4

E-5-((3-phenoxy)thiophen-2-ylmethylene)-2-thioxo-3-ethyl-thiazolidin-4-one

3-Phenoxythiophen-2-carboxaldehyde (204mg, 1.44mmol) and 2-thioxo-3-ethyl-thiazolidin-4-one (231mg, 1.44mmol) are stirred together in 1.44mL of a 1:1 (V:V) mixture of acetic acid and N,N-dimethylacetamide containing sodium acetate (59mg, 0.72mmol) for 50 hours at 90°C under argon. After cooling to ambient temperature, water (10mL) is added to the reaction mixture. The resulting precipitate is isolated by filtration and washed with 100mL water, then air-dried and dried under high vacuum, yielding 443mg (88%) of the title compound.

^{1}HNMR (500MHz, $CDCl_3$):

δ: 8.09 1Hs, 7.61 1Hd (J=5.5 Hz), 7.37 2Ht (J=8.1), 7.17 1Ht (J=7.3 Hz), 7.05 2Hd (J=7.8 Hz), 6.75 1Hd (J=5.3 Hz), 4.18 2Hq (J=7.0 Hz), 1.27 3Ht (J=7.2 Hz).

Example 5

E-5-(5-(2-nitrophenyl)furan-2-ylmethylene)-2-thioxo-3-ethyl-thiazolidin-4-one

5-(2-nitrophenyl)furan-2-carboxaldehyde and 2-thioxo-3-ethyl-thiazolidin-4-one are converted to the title compound generally according to the protocol of Example 4.

^{1}HNMR (500MHz, $CDCl_3$):

δ: 7.86 1Hd (J=8.6), 7.8 1Hd (J=8.4), 7.71 1Ht (J=7.8), 7.54 1Ht (J=7.7), 7.46 1Hs, 6.93 1Hd (J=4.0), 6.83 1Hd (J=4.1 Hz), 4.19 2Hq (J=7.2), 1.28 3Ht (J=7.2).

Example 6

E-5-(2,3,4-trimethoxy-benzylidene)-2-thioxo-3-ethyl-thiazolidin-4-one

2,3,4-trimethoxybenzaldehyde and 2-thioxo-3-ethyl-thiazolidin-4-one are converted to the title compound generally according to the protocol of Example 4.

^{1}HNMR (500MHz, $CDCl_3$):

δ: 7.99 1Hs, 7.15 1Hd (J=9.1 Hz), 6.77 1Hd (J=8.5 Hz), 4.2 2Hq (J=7.2Hz), 3.3Hs, 3.93 3Hs, 3.88 3Hs, 1.29 3Ht (J=7.2 Hz).

Example 7

E-5-(5-(2-nitrophenyl)-2-furan2-ylmethylene)-2-thioxo-3-allyl-thiazolidin-4-one

5-(2-nitrophenyl)furan-2-carboxaldehyde (77mg, 0.45mmol) and 2-thioxo-3-ethyl-thiazolidin-4-one (72mg, 0.45mmol) are stirred together in 0.46mL of a 1:1 (V:V) mixture of acetic acid and N,N-dimethylacetamide containing sodium acetate (18.5mg, 0.225mmol) at 90°C under argon for 86 hours. After cooling to 25°C, water (40mL) is added to the reaction mixture, and the resulting precipitate is isolated by filtration and washed with 100mL water, air dried, and dried under high vacuum, yielding 161mg (100%) of the title compound.

^{1}HNMR (500MHz, $CDCl_3$):

δ: 7.87 1Hd (J=8.6Hz), 7.8 1Hd (J=8.4Hz), 7.54 1Ht (J=7.7Hz), 7.54 1Ht (J=7.7Hz), 7.47 1Hs, 6.94 1Hd (J=3.5Hz), 6.83 1Hd (J=3.9Hz), 5.86 1Hm, 5.29 1Hd (J=18Hz), 5.25 1Hd (J=10.3Hz), 4.74 2Hd (J=6.3Hz).

Example 8

E-5-(5-(2-nitrophenyl)-2-furan2-ylmethylene)-thiazolidin-2,4-dione

5-(2-nitrophenyl)furan-2-carboxaldehyde and thiazolidin-2,4-dione are combined using the protocol of Example 7 to yield the title compound.

^{1}HNMR (500MHz, DMSO-d_6):

δ: 12.5 1Hs, 8 1Hd (J=7.9Hz), 7.93 1Hd (J=7.8Hz), 7.83 1Ht (J=7.6Hz), 7.68 1Ht (J=7.9Hz), 7.62 1Hs, 7.26 1Hd (J=3.7Hz), 7.22 1Hd (J=3.7Hz).

Example 9

E-6-(5-(5-(2-nitrophenyl)-2-furanylidene)-4-oxo-2-thioxo-thiazolidin-3-yl)-hexanoic acid isopropyl ester

5-(2-nitrophenyl)furan-2-carboxaldehyde and 6-(4-oxo-2-thioxo-thiazolidin-3-yl)-hexanoic acid isopropyl ester are combined using the protocol of Example 7 to yield the title compound.

^{1}HNMR (500MHz, $CDCl_3$):

δ: 7.87 1Hd (J=8.6Hz), 7.80 1Hd (J=8.2Hz), 7.54 1Ht (J=7.8Hz), 7.54 1Ht (J=7.8), 7.46 1Hs (J=7.3Hz), 6.93 1Hd (J=4.0Hz), 6.83 1Hd (J=3.7Hz), 5.0 1Hm, 4.11 2Ht (J=7.6Hz), 2.28 2Ht (J=7.3Hz), 1.70 4Hm, 1.40 2Hm, 1.22 6Hd (J=6.2Hz)

Example 10

E-5-(5-(2-chlorophenyl)furan-2-ylmethylene))-2-thioxo-3-ethyl-thiazolidin-4-one

5-(2-chlorophenyl)furan-2-carboxaldehyde and 2-thioxo-3-ethyl-thiazolidin-4-one are combined using the protocol of Example 1 to yield the title compound.

^{1}HNMR (500MHz, $CDCl_3$):

δ: 8.00 1Hdd (J1=7.4Hz, J2=1.8Hz), 7.47 3Hm, 7.38 1Hd (J=3.9Hz), 7.32 1Ht (J=7.9Hz), 6.98 1Hd (J=3.2Hz), 4.21 2Hq (J=7.2Hz), 1.3 3Ht (J=6.9Hz).

Example 11

E-5-(5-(2-trifluoromethyl)furan-2-ylmethylene))-2-thioxo-3-ethyl-thiazolidin-4-one

5-(2-trifluoromethyl)furan-2-carboxaldehyde and 2-thioxo-3-ethyl-thiazolidin-4-one are combined using the protocol of Example 1 to yield the title compound.

^{1}HNMR (500MHz, $CDCl_3$):

δ: 7.94 1Hd (J=7.9Hz), 7.81 1Hd (J=7.9Hz), 7.72 1Ht (J=7.7Hz), 7.54 1Ht (J=7.7Hz), 7.47 1Hs, 2Hs, 4.2 2Hq (J=7.2Hz), 1.29 3Ht (J=7.2Hz).

Example 12

E-5-(5-(2-methoxycarbonylthiophen-3-yl)furan-2-ylmethylene))-2-thioxo-3-ethyl-thiazolidin-4-one

5-(2-methoxycarbonylthiophen-3-yl)furan-2-carboxaldehyde (63mg, 0.39mmol) and 2-thioxo-3-ethyl-thiazolidin-4-one (91mg, 0.39mmol) are stirred in 0.44mL dimethylacetamide and 0.19mL acetic acid containing sodium acetate (32mg, 0.39mmol) for 67 hours at 85°C under an argon atmosphere. Cold water (7mL, 5°C) is added to the reaction mixture, resulting in a precipitate.

After filtration and washing with 15 mL cold water, the residue is dissolved in 24mL of 9:1 methylene chloride, filtered and stripped of solvent under high vacuum. Yield: 50mg (34%).

^{1}HNMR (500MHz, $CDCl_3$):

δ: 7.81 1Hd (J=4Hz), 7.73 1Hd (J=5.1Hz), 7.6 1Hd (J=5.2Hz), 1Hs (J=Hz), 6.97 1Hd (J=4Hz), 4.2 2Hq (J=7.2Hz), 3.92 3Hs, 1.3 3Ht (J=7.2Hz).

Example 13

5-(2-(furan-2-yl)eth-1-enylmethylene))-2-thioxo-3-ethyl-thiazolidin-4-one

3-(furan-2-yl)propenal and 2-thioxo-3-ethyl-thiazolidin-4-one are combined using the protocol of Example 1 to yield the title compound.

^{1}HNMR (500MHz, DMSO-d_6):

δ: 7.52 1Hd (J=1.4Hz), 7.37 1Hd (J=11.9Hz), 6.82 1Hd (J=14.8Hz), 6.64 1Hdd (J=11.6Hz, 14.7Hz)), 6.6 1Hd (J=3.6Hz), 6.5 1Ht (J=2.4Hz), 4.16 2Hq (J=7.2Hz), 1.27 3Ht (J=6.9Hz).

Example 14

E-5-(3-(4-methoxyphenoxy)-benzylidene)-2-thioxo-3-ethyl-thiazolidin-4-one

3-(4-Methoxyphenoxy)-benzaldehyde and 2-thioxo-3-ethyl-thiazolidin-4-one are converted to the title compound using the protocol of Example 1.

^{1}HNMR (500MHz, $CDCl_3$):

δ: 7.78 1Hs, 7.52 1Ht (J=Hz), 7.33 1Hd (J=Hz), 7.13 1Ht (J=Hz), 7.08 3Hm, 7.01 2Hd (J=8.0Hz), 4.05 2Hq (J=7.0Hz), 3.77 3Hs, 1.18 3Ht (J=6.8Hz).

Example 15

E-3-(2-furylmethyl)-5-{[5-(2-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one

5-(2-nitrophenyl)furan-2-carboxaldehyde and 3-(2-furylmethyl)-2-thioxo-1,3-thiazolidin-4-one are combined using the protocol of Example 7 to yield the title compound.

^{1}HNMR (500MHz, $CDCl_3$):

δ: 7.85 1Hd (J=8.0Hz), 7.80 1Hd (J=8.1Hz), 7.70 1Ht (J=7.7Hz), 7.54 1Ht (J=7.7Hz), 7.35 1Hs, 6.94 1Hd (J=3.7Hz), 6.82 1Hd (J=3.4Hz), 6.42 1Hd (J=3.1Hz), 6.32 1Ht (J=2.3Hz), 5.31 2Hs.

Example 16

5-(2-methyl-3-phenylprop-2-enylidene)-3-ethyl-2-thioxo-1,3-thiazolidin-4-one

2-methyl-3-phenylprop-2-enal and 3-ethyl-2-thioxo-1,3-thiazolidin-4-one are combined using the protocol of Example 7 to yield the title compound.

^{1}HNMR (500 MHZ, $CDCl_3$):

δ: 7.52 1Hs, 7.37 5Hm, 7.06 1Hs, 4.19 2Hq (J=7.2Hz), 2.24 3Hs, 1.28 3Ht (J=7.2Hz).

Example 17

E-3-ethyl-5-{[3-(phenylmethoxy)phenyl]methylene}-2-thioxo-1,3-thiazolidin-4-one

3-(phenylmethoxy)benzaldehyde (402mg, 1.89mmol) and 3-ethyl-2-thioxo-1,3-thiazolidin-4-one (317mg, 1.97mmol) are dissolved in 1mL dimethylacetamide and 1mL acetic acid containing sodium acetate (89mg, 1.085mmol). The mixture is stirred under argon at 90°C for 40 hours, cooled to ambient temperature, and treated with 20mL water to precipitate the product. The mixture is filtered and the residue washed with 100mL water, air dried, and dried under high vacuum to yield 576 mg of the title product (82% based on 3-(phenylmethoxy)benzaldehyde).

^{1}HNMR (500MHz, $CDCl_3$):

δ: 7.67 1Hs, 7.40 6Hm, 7.08 3Hm, 5.12 2Hs, 4.19 2Hq (J=7.1Hz), 1.29 3Ht, (J=7.2Hz).

Example 18

E-3-ethyl-5-{[5-(3-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one

5-(3-nitrophenyl)furan-2-carboxaldehyde (132mg, 0.61mmol) and 3-ethyl-2-thioxo-1,3-thiazolidin-4-one (98mg, 0.61mmol) are stirred in 0.91mL dimethylacetamide and 0.3mL acetic acid containing sodium acetate (50mg, 0.61mmol) for 67 hours at 85°C under an argon atmosphere. Cold water (7mL, 5°C) is added to the reaction mixture, resulting in a precipitate. After filtration and washing with 15mL cold water, the residue is dissolved in 24mL of 9:1 methylene chloride, filtered and stripped of solvent under high vacuum. Yield: 116mg (52 %)

^{1}HNMR (500MHz, $CDCl_3$):

δ: 7.85 1Hd (J=8.0Hz), 7.80 1Hd (J=8.1Hz), 7.70 1Ht (J=7.7Hz), 7.54 1Ht (J=7.7Hz), 7.35 1Hs, 6.94 1Hd (J=3.7Hz), 6.82 1Hd (J=3.4Hz), 6.42 1Hd (J=3.1Hz), 6.32 1Ht (J=2.3Hz), 5.31 2Hs.

Example 19

E-5-{[3,5-bis(tert-butyl)-4-hydroxyphenyl]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one

3,5-bis(tert-butyl)-4-hydroxybenzaldehyde and 3-methyl-2-thioxo-1,3-thiazolidin-4-one are combined using the protocol of Example 12 to yield the title compound.

^{1}HNMR (500MHz, $CDCl_3$):

δ: 7.73 1Hs, 7.36 2Hs, 5.74 1Hs, 3.52 3Hs, 1.48 18Hs.

Example 20

E-5-({3-[4-(tert-butyl)phenoxy]phenyl}methylene)-3-methyl-2-thioxo-1,3-thiazolidin-4-one

3-[4-(tert-butyl)phenoxy]benzaldehyde and 3-methyl-2-thioxo-1,3-thiazolidin-4-one are combined using the protocol of Example 1 to yield the title compound.

^{1}HNMR (500MHz, $CDCl_3$):

δ: 7.67 1Hs, 7.41 3Hm, 7.19 1Hd (J=7.8Hz), 7.08 1Hdd (J=8.2Hz), 7.05 1Ht (J=1.8Hz), 6.98 2Hdd (J=6.4Hz), 3Hs, 1.35 9Hs.

The following Examples describe the synthesis of compounds according to the present invention which are not purified, nor characterized according to NMR spectra. The crude, uncharacterized product will then be screened in a preliminary TNF/TNF receptor binding assay (see Example 42):

Example 21

3-ethyl-5-(1,3-thiazol-2-ylmethylene)-2-thioxo-1,3-thiazolidin-4-one

3-ethyl-2-thioxo-1,3-thiazolidin-4-one and 1,3-thiazol-2-carboxaldehyde are combined using the protocol of Example 1 to yield the title compound.

Example 22

5-(2-methyl-3-phenylprop-2-enylidene)-3-methyl-2-thioxo-1,3-thiazolidin-4-one

3-methyl-2-thioxo-1,3-thiazolidin-4-one and 2-methyl-3-phenylpropenal are combined using the protocol of Example 4 to yield the title compound.

Example 23

3-ethyl-5-{[3-(2-hydroxyethoxy)phenyl]methylene}-2-thioxo-1,3-thiazolidin-4-one

3-ethyl-2-thioxo-1,3-thiazolidin-4-one and 3-(2-hydroxyethoxy)benzaldehyde are combined using the protocol of Example 4 to yield the title compound.

Example 24

3-methyl-5-{[3-(4-methylphenoxy)phenyl]methylene}-2-thioxo-1,3-thiazolidin-4-one

3-methyl-2-thioxo-1,3-thiazolidin-4-one and 3-(4-methylphenoxy)benzaldehyde are combined using the protocol of Example 4 to yield the title compound.

Example 25

3-methyl-5-{[5-(3-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one

3-methyl-2-thioxo-1,3-thiazolidin-4-one and 5-(3-nitrophenyl)2-furaldehyde are combined using the protocol of Example 1 to yield the title compound.

Example 26

5-(5-{2-nitrophenylfuran-2-ylmethylene})-2-thioxo-3-methyl-thiazolidin-4-one

3-methyl-2-thioxo-1,3-thiazolidin-4-one and 5-(2-nitrophenyl)2-furaldehyde are combined using the protocol of Example 4 to yield the title compound.

Example 27

3-ethyl-5-{[3-(4-methylphenoxy)phenyl]methylene}-2-thioxo-1,3-thiazolidin-4-one

3-ethyl-2-thioxo-1,3-thiazolidin-4-one and 3-(4-methylphenoxy)benzaldehyde are combined using the protocol of Example 4 to yield the title compound.

Example 28

5-{[3-(4-methoxyphenoxy)phenyl]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one

3-methyl-2-thioxo-1,3-thiazolidin-4-one and 3-(4-methoxyphenoxy)benzaldehyde are combined using the protocol of Example 4 to yield the title compound.

Example 29

5-({3-[4-methylphenoxy]phenyl}methylene)-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one

3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one and 3-(4-methylphenoxy)benzaldehyde are combined using the protocol of Example 1 to yield the title compound.

Example 30

5-{[3,5-bis(tert-butyl)-4-hydroxyphenyl]methylene}-3-ethyl-2-thioxo-1,3-thiazolidin-4-one

3-ethyl-2-thioxo-1,3-thiazolidin-4-one and 3,5-bis(tert-butyl)-4-hydroxybenzaldehyde are combined using the protocol of Example 4 to yield the title compound.

Example 31

5-({3-[4-methoxyphenoxy]phenyl}methylene)-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one

3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one and 3-[4-methoxyphenoxy]benzaldehyde are combined using the protocol of Example 1 to yield the title compound.

Example 32

5-({3-[4-(tert-butyl)phenoxy]phenyl}methylene)-3-ethyl-2-thioxo-1,3-thiazolidin-4-one

3-ethyl-2-thioxo-1,3-thiazolidin-4-one and 3-[4-(tert-butyl)phenoxy]benzaldehyde are combined using the protocol of Example 1 to yield the title compound.

Example 33

3-ethyl-5-{[5-(2-trifluoromethoxyphenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one

3-ethyl-2-thioxo-1,3-thiazolidin-4-one and 5-(2-trifluoromethoxyphenyl)2-furaldehyde are combined using the protocol of Example 4 to yield the title compound.

Example 34

5-({3-[4-(tert-butyl)phenoxy]phenyl}methylene)-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one

3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one and 3-[4-(tert-butyl)phenoxy]benzaldehyde are combined using the protocol of Example 1 to yield the title compound.

Example 35

5-({2,5-dimethyl-1-[3-(trifluoromethyl)phenyl]pyrrol-3-yl}methylene)-3-ethyl-2-thioxo-1,3-thiazolidin-4-one

3-ethyl-2-thioxo-1,3-thiazolidin-4-one and 2,5-dimethyl-1-[3-(trifluoromethyl)phenyl] pyrrol-3-carboxaldehyde are combined using the protocol of Example 4 to yield the title compound.

Example 36

3-(3-hydroxyphenyl)-5-{[5-(2-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one

3-(3-hydroxyphenyl)-2-thioxo-1,3-thiazolidin-4-one and 5-(2-nitrophenyl)(2-furaldehyde) are combined using the protocol of Example 4 to yield the title compound.

Example 37

3-(4-ethoxyphenyl)-5-{[5-(2-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one

3-(4-ethoxyphenyl)-2-thioxo-1,3-thiazolidin-4-one and 5-(2-nitrophenyl)(2-furaldehyde) are combined using the protocol of Example 4 to yield the title compound.

Example 38

5-{[3,5-bis(phenylmethoxy)phenyl]methylene}-3-ethyl-2-thioxo-1,3-thiazolidin-4-one-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one

3-ethyl-2-thioxo-1,3-thiazolidin-4-one and 3,5-bis(phenylmethoxy)benzaldehyde are combined using the protocol of Example 4 to yield the title compound.

Example 39

3-methyl-5-(1,3-thiazol-2-ylmethylene)-2-thioxo-1,3-thiazolidin-4-one

3-methyl-2-thioxo-1,3-thiazolidin-4-one and 1,3-thiazole-2-carboxaldehyde are combined using the protocol of Example 1 to yield the title compound.

Example 40

5-[(5-methyl(2-furyl))methylene]-3-ethyl-2-thioxo-1,3-thiazolidin-4-one

3-ethyl-2-thioxo-1,3-thiazolidin-4-one and 5-methyl-2-furaldehyde are combined using the protocol of Example 4 to yield the title compound.

Example 41

5-[4-({[2-(5-formyl-2-thienyl)-1,3-dioxolan-4-yl]methoxy}methyl) polystyrene

To 60mL of (2,2-dimethyl-1,3-dioxolan-4-yl)methan-1-ol, thiophene-2-carbaldehyde is added 2g (0.0833 mmol) of Sodium. After stirring at 25°C under argon, 7g of chloromethyl polystyrene/divinylbenzene copolymer (1% cross linked, 0.8mmol Cl per gram of resin) is added and stirred overnight at 25°C, then at 80°C for 24 hours. The resin is washed 3 times with 25mL Dioxane, 3 times with 25mL

dioxone/H_2O, 6 times with 25mL H_2O, 3 times with 25mL EtOH, 3 times with 25mL MeOH, and dried under high vacuum. The resin is then treated with a 1/1 mixture of dioxane and 1M HCl [concentrated] for 48 hours at 25°C. The resin is again washed with 3 times with 25mL Dioxane, 3 times with 25mL H_2O, 3 times with 25mL Dioxane, 3 times with 25mL Acetone, 3 times with 25mL EtOH, 3 times with 25mL MeOH and dried in vacuo.

A portion (2g, 1.6mmols of diol) of the resulting product (2,2-dimethyl(1,3-dioxolan-4-yl))methoxy]methyl polystyrene) is stirred overnight at 85°C with 4.9g (3.5mmol) of 2.5,-thiophone dicarbaldehyde dissolved in a minimum volume of toluene, 1g (8.3mmol) of anhydrous magnesium sulfate, 0.1g (0.526mmol) Toluenesulfonic Acid. The resin is washed 2 times with 25mL pyridine, 3 times with 25mL pyridine/H_2O, 6 times with 25mL H_2O, 3 times with 25mL EtOH, 3 times with 25mL MeOH, and dried in vacuo to yield the title compound.

Example 42

2-(5-formyl-2-thienyl)acetic acid

To 1g (0.8mmol of aldehyde) of the product from Example 41 (5-[4-({[2-(5-formyl-2-thienyl)-1,3-dioxolan-4-yl]methoxy}methyl) polystyrene) is added 15mL THF, 1mL (2.4 mmol) of 40% benzyltrimethhylammonium hydroxide in water, and 3mL (28.8 mmol) of methyl (methylsulfinal) sulfoxide. This mixture is stirred in a capped vial at 60°C overnight. The resin mix is cooled, then filtered and washed 3 times with 25mL THF, 3 times with 25mL Dioxane, 3 times with 25mL MeOH, 3 times with 25mL Dioxane, 3 times with 25mL MeOH, and dried in vacuo. The product resin (1g) is then treated with a solution of 8mL conc. HCl in 8mL Dioxane for 3 hours at 25°C. To this solution is added 10mL of dichloromethane and 1mL H_2O. The filtrate is collected and the resin is washed 3 times with 2mL of dichloromethane followed by 5mL of H_2O. The resulting filtrates are all combined and the organic layers separated. The aqueous layer is extracted with dichloromethane, the organic layers are combined,

dried with sodium sulfate, and evaporated to give an oily residue which is dissolved in ether then extracted with saturated $KHCO_3$. The aqueous layer is acidified with HCl and extracted with DCM dried and evaporated to yield 41mg of the title product (30% based on the resin from Example 41).

Example 43

N-[(5-formyl-2-thienyl)methyl]acetamide

To 1g (0.8 mmole of aldehyde) of the product from Example 41 (5-[4-({[2-(5-formyl-2-thienyl)-1,3-dioxolan-4-yl]methoxy}methyl) polystyrene) is added trimethyl orthoformate containing 2% acetic acid (the minimum volume sufficient to allow stirring of the slurry). Ammonium acetate (231mg, 3mmol) is then added and the mixture is stirred for 20 minutes at 25°C. Sodium cyanoborohydride (188.5mg, 3mmol) is added and the mixture is stirred at 25°C in a sealed vial for 18 hours. The resin is washed 2 times with 15mL of trimethylorthoformate, 3 times with 15mL of pyridine, 3 times with 15mL of DMF, 3 times with 15mL of dichloromethane, 3 times with 15mL of MeOH, 2 times with 15mL of dichloromethane, 3 times with 15mL of MeOH and dried in vacuo. The resin is then taken up in 15mL of a 20% acetic anhydride in dichloromethane containing 0.5mL of diisopropylethylamine and stirred for 2 hours. The resin is treated with Dioxane/1M HCl (conc.) (1/1) for 48 hours, then diluted with H_20, filtered and extracted with DCM (15mLx3). The filtrates are combined, the organic layer is isolated, dried with sodium sulfate, and evaporated in vacuo to give 50mg of the title product (34% yield based on the resin from Example 41).

Example 44

5-(hydroxymethyl)thiophene-2-carbaldehyde

To 0.5g of 2.5 thiophene dicarbaldehyde (3.57mmol) in 25mL EtOH is added 1mmol (38 mg) sodium borohydride. The soln is stirred for 2 hours, monitoring by TLC using 50/50 hexane/ethyl acetate. The reaction is quenched with 10mL water and extracted 3 times with 10mL dichloromethane. The organic layers are combined, dried over magnesium sulfate and evaporated to yield 420mg of product as a pale yellow oil (83% yield).

Example 45

5-[(methylsulfonyl)methyl]thiophene-2-carbaldehyde

To 0.420 mg (2.95mmol) of 5-(hydroxymethyl)thiophene-2-carbaldehyde is added drop wise 322mg (1.19mmol) of phosphorous tribromide at –5°C. This reaction mixture is stirred and allowed to rise to 25°C over 1 hour. When the starting material is gone (monitored by TLC), the mixture is diluted with ~2mL DCM and run through a short plug of silica gel using 100% hexane followed by 90/10 (hexane/ethyl acetate). The first fraction is collected and evaporated to give 360mg of a yellow/green oil, which is used without further purification.

To 120mg of the crude 5- bromomethyl-2-thiophenecarbaldehyde in 10mL dichloroethane is added 120mg of sodium methyl thiosulfinate. The reaction is heated to 80°C under argon overnight (~16 hours). The reaction is cooled to 25°C and washed with 30mL H_2O and extracted with three 10mL portions of dichloroethane. The combined organic phases are dried over magnesium sulfate, evaporated, dissolved in 20% ethyl acetate/80% hexane, filtered through silica, and evaporated to give 42mg of the title product (21% based on 5-(hydroxymethyl)thiophene-2-carbaldehyde).

Example 46

5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carbaldehyde

2.38g (13.6mmol) 5-bromothiophene-2-carbaldehyde, 3.11g (12.2mmol) of 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl(1,3,2-dioxaborolan-2-yl))-1,3,2-dioxaborolane, 3.6g (36.7mmol) of potassium acetate and 0.33g (0.404mmol) of [1,1'bis(diphenylphosphino)-ferrocene]dichloropalladium (II) are combined in 80mL of DMF and heated under argon with stirring at 75°C for 18 hours. After cooling to 25°C, the solution is filtered, stripped of the solvent in vacuo and dissolved in 136mL ethoxyethanol to yield a 0.1M solution of the title compound. The crude product is stored at –20°C and used without purification for the subsequent steps.

Example 47

5-[4-(phenylmethoxy)phenyl]furan-2-carbaldehyde

5mL (0.5mmol) of the product from Example 46 in ethoxyethanol, 132mg (0.5mmol) of 4-benzyloxyphenyl bromide, 10.5mg (0.015mmol) dichlorobis(triphenylphosphine)palladium(II), and 0.75mL of a 2M aqueous solution of potassium carbonate (1.5mmol) are combined, degassed with argon, and heated to 100°C for 18 hours under argon. The reaction mixture is cooled to 25°C, stripped of solvent and purified using silica gel chromatography with ethyl acetate/hexane as the eluant to yield 47mg (34%) of the title compound.

Example 48

3-cyclopentyl-N-(4-oxo-2-thioxo(1,3-thiazolidin-3-yl))propanamide

A solution of 262mg (1mmol) triphenylphosphine in dichloromethane (0.5mL) is cooled to 0°C and a solution of 133.5mg (1mmol) of N-chlorosuccinimide in 0.5mL dichloromethane is added dropwise with stirring. The solution is allowed to warm to 25°C and 142mg (1mmol) of 3-cyclopentylpropionic acid in 0.5mL dichloromethane is added dropwise. The mixture is cooled to 0°C and N-amino rhodanine (148mg, 2mmol) dissolved in 2mL of THF is added. The reaction mixture is stirred for 18

hours while allowing it to warm to 25°C. The solvent is evaporated, the residue is dissolved in ether, filtered, and washed twice with aqueous potassium carbonate. The ether layer is dried with magnesium sulfate, filtered, stripped of solvent and partially purified on silica gel using hexane/ethyl acetate to yield 230mg of crude product, containing 40% triphenylphosphine oxide. The product is used for subsequent steps without further purification.

Example 49

N-(4-oxo-2-thioxo(1,3-thiazolidin-3-yl))hexanamide

Hexanoic acid and N-amino rhodanine are combined using the procedure in Example 48 to form the title compound.

Example 50

N-(4-oxo-2-thioxo(1,3-thiazolidin-3-yl))cyclohexanecarboxamide

Cyclohexanecarboxylic acid and N-amino rhodanine are combined using the procedure in Example 48 to form the title compound.

Example 51

N-(4-oxo-2-thioxo(1,3-thiazolidin-3-yl))-4-methyl benzamide

4-Methylbenzoic acid and N-amino rhodanine are combined using the procedure in Example 48 to form the title compound.

Example 52

5-[4-(phenylmethylthio)phenyl]furan-2-carbaldehyde

4-(phenylmethylthio)bromobenzene and the product from Example 46 are combined according to the procedure in Example 47 to form the title compound.

Example 53

5-[3-phenylphenyl]furan-2-carbaldehyde

3-Bromobiphenyl and the product from Example 46 are combined according to the procedure in Example 47 to form the title compound.

Example 54

5-(2-acetamidophenyl)furan-2-carbaldehyde

2-Acetamidophenylboronic acid and 5-bromofuraldehyde are combined according to the procedure in Example 47 to form the title compound.

Example 55

5-Cyanothiophene-2-carboxaldehyde

2,5-thiophenedicarboxaldehyde (541mg, 3.86mmol) and hydroxylamine hydrochloride (402.34mg, 5.789mmol) are dissolved in 12mL of 1:1 pyridine/1-butanol and heated to 90°C for 28 hours. The solvent is removed by warming under a stream of argon followed by high vacuum. The crude product is diluted to a volume of 4mL with dimethylacetamide to produce a solution containing 0.48mol/liter of the title compound. This solution is used without purification in subsequent steps.

Example 56

(5-formyl-2-thienyl)methylamine

To 1g (0.8mmole of aldehyde) of the product from Example 41 (5-[4-({[2-(5-formyl-2-thienyl)-1,3-dioxolan-4-yl]methoxy}methyl) polystyrene) is added trimethyl orthoformate containing 2% acetic acid (the minimum volume sufficient to allow stirring of the slurry). Ammonium acetate (231 mg, 3mmol) is then added and the mixture is stirred for 20 minutes at 25°C. Sodium cyanoborohydride (188.5mg, 3mmol) is added and the mixture is and stirred at 25°C in a sealed vial for 18 hours.

The resin is washed 2 times with 15mL of trimethylorthoformate, 3 times with 15mL of pyridine, 3 times with 15mL of DMF, 3 times with 15mL of dichloromethane, 3 times with 15mL of MEOH, 2 times with 15mL of dichloromethane, 3 times with 15mL of MeOH and dried *in vacuo*. The resin is treated with Dioxane/1M HCl (conc.) (1/1) for 48 hours, then diluted with H_2O, filtered and extracted with DCM (15mL x 3). The filtrates are combined and neutralized with potassium hydrogen carbonate. The organic layer is isolated, dried with sodium sulfate, and evaporated *in vacuo* to give the title product

Example 57

3-(4-chlorophenethyl)-5-[(5-methyl-2-furyl)methylene]-2-thioxo-1,3-thiazolan-4-one

Commercially available compound.

Example 58

Methyl 3-{5-[(3-ethyl-4-oxo-2-thioxo(1,3-thiazolidin-5-ylidene))methyl](2-furyl)}-4-methylthiophene-2-carboxylate

Methyl (3-(5-formylfuryl)-4-methyl)thiophene-2-carboxylate and N-ethylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 59

5-((2E)-3-(2-furyl)prop-2-enylidene)-3-(2-furylmethyl)-2-thioxo-1,3-thiazolidin-4-one

3-(2-Furyl)prop-1-ene-3-al and N-(2-furylmethyl)rhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 60

5-[(2E)-3-(2-methoxyphenyl)prop-2-enylidene]-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one

3-(2-Methoxyphenyl)prop-1-ene-3-al and N-allylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 61

Methyl 3-{5-[(4-oxo-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}thiophene-2-carboxylate

Methyl (3-(5-formylfuryl)thiophene-2-carboxylate and N-allylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 62

5-[(2E)-3-(2-nitrophenyl)prop-2-enylidene]-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one

3-(2-Nitrophenyl)prop-1-ene-3-al and N-allylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 63

5-{[5-(2-chlorophenyl)(2-furyl)]methylene}-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one

5-(2-chlorophenyl)furan-2-carbaldehyde and N-allylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 64

5-{[5-(3-chlorophenyl)(2-furyl)]methylene}-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one

5-(3-chlorophenyl)-furan-2-carbaldehyde and N-allylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 65

5-({5-[2-nitro-4-(trifluoromethyl)phenyl](2-furyl)}methylene)-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one

5-(4-trifluoromethyl-2-nitrophenyl)-furan-2-carbaldehyde and N-allylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 66

Methyl 3-{5-[(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}thiophene-2-carboxylate

Methyl (3-(5-formylfuryl)thiophene-2-carboxylate and rhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 67

Ethyl 2-(5-{[5-(2-chlorophenyl)(2-furyl)]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetate

5-(2-Chlorophenyl)-furan-2-carbaldehyde and ethyl 2-(4-oxo-2-thioxo-1,3-thiazolidin-3-yl) acetate are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 68

5-((2E)-3-(2-furyl)-2-phenylprop-2-enylidene)-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one

2-Phenyl-3-(2-furyl)-propenal and N-allylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 69

5-(Benzo[d]furan-2-ylmethylene)-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one

Benzo[d]furan-2-carbaldehyde and N-allylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 70

5-{[5-(2,5-dichlorophenyl)(2-furyl)]methylene}-3-ethyl-2-thioxo-1,3-thiazolidin-4-one

5-(2,5-dichlorophenyl)-furan-2-carbaldehyde and N-ethylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 71

5-{[5-(2,4-Dichlorophenyl)(2-furyl)]methylene}-3-ethyl-2-thioxo-1,3-thiazolidin-4-one

5-(2,4-dichlorophenyl)-furan-2-carbaldehyde and N-ethylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 72

3-Ethyl-5-[(5-methyl(2-thienyl))methylene]-2-thioxo-1,3-thiazolidin-4-one

5-methylthiophene-2-carbaldehyde and N-ethylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 73

{5-[(3-Ethyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}methyl acetate

5-(acetoxymethyl)furan-2-carbaldehyde and N-ethylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 74

5-{[5-(4-chlorophenylthio)(2-furyl)]methylene}-3-ethyl-2-thioxo-1,3-thiazolidin-4-one

5-(4-chlorophenylthiofuran-2-carbaldehyde and N-ethylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 75

N-(5-{[5-(2-nitrophenyl)(2-furyl)]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetamide

5-(2-nitrophenyl)furan-2-carbaldehyde and N-(acetylamino)rhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 76

5-((2E)-3-(2-furyl)prop-2-enylidene)-3-methyl-2-thioxo-1,3-thiazolidin-4-one

3-(2-furyl)propenal and N-methylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 77

3-methyl-5-[(5-methyl(2-thienyl))methylene]-2-thioxo-1,3-thiazolidin-4-one

5-methylthiophene-2-carbaldehyde and N-methylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 78

5-{[5-(2-trifluoromethylphenyl)(2-furyl)]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one

5-(2-trifluoromethylphenyl)furan-2-carbaldehyde and N-methylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 79

5-{[5-(2-chlorophenyl)(2-furyl)]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one

5-(2-chlorophenyl) furan-2-carbaldehyde and N-methylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 80

3-methyl-5-[(5-(2-thienyl)(2-thienyl))methylene]-2-thioxo-1,3-thiazolidin-4-one

5-thiophenylthiophene-2-carbaldehyde and N-methylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 81

N-[4-oxo-5-({5-[4-(phenylmethoxy)phenyl](2-furyl)}methylene)-2-thioxo-1,3-thiazolidin-3-yl]hexanamide

The product from Example 47 and the product from Example 49 are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 82

Cyclohexyl-N-(5-{[5-(3-nitrophenyl)(2-furyl)]methylene}-4-oxo-2-thioxo(1,3-thiazolidin-3-yl))carboxamide

The product from Example 50 and 5-(3-nitrophenyl)furan-2-carbaldehyde are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 83

3-ethyl-5-({5-[4-(phenylmethoxy)phenyl](2-furyl)}methylene)-2-thioxo-1,3-thiazolidin-4-one

The product from Example 47 and N-ethylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 84

cyclohexyl-N-[4-oxo-5-({5-[4-(phenylmethylthio)phenyl](2-furyl)}methylene)-2-thioxo(1,3-thiazolidin-3-yl)]carboxamide

The product from Example 50 and the product from Example 52 are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 85

5-[(3-ethyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]thiophene-2-carbaldehyde

2,5-thiophenedicarboxaldehyde (283 mg, 2.02mmol) and 3.03mL of a 1M solution of 3-ethylrhodanine are combined in 1:1 dimethylacetamide/acetic acid containing 0.5M sodium acetate, and stirred under argon for 16 hours at 70°C. Water (200mL) and diethyl ether (200mL) are added, and the phases separated. Extracted the aqueous phase with 2 x 100mL ether, combined all organic phases, and extracted the organic phases with 3 x 100mL water and 1 x 100mL saturated aqueous sodium chloride. The organic layer is dried with magnesium sulfate, filtered and stripped of solvent to yield the title compound.

Example 86

5-[(3-methyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]thiophene-2-carbaldehyde

Combined 2,5-thiophenedicarboxaldehyde (69.1mg, 0.49mmol) and a 0.74mL of a 1M solution of 3-ethylrhodanine in 1:1 dimethylacetamide/acetic acid containing 0.5M sodium acetate. Stirred under argon for 19 hours at 85°C. Cooled to 25°C, added 100mL of water, filtered and washed the residue with 200mL water and dried *in vacuo*. The crude product is dissolved in DMSO and filtered- to yield the title compound as a solution in DMSO.

Example 87

Methylethyl 6-{5-[(5-methyl(2-furyl))methylene]-4-oxo-2-thioxo-1,3-thiazolidin-3-yl}hexanoate

Methylethyl 6-{4-oxo-2-thioxo-1,3-thiazolidin-3-yl}hexanoate and 5-methylfuran-2-carbaldehyde are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 88

5-((2E)-3-(2-furyl)prop-2-enylidene)-3-[2-(3,4-dimethoxyphenyl)ethyl]-2-thioxo-1,3-thiazolidin-4-one

3-[2-(3,4-dimethoxyphenyl)ethyl]-2-thioxo-1,3-thiazolidin-4-one and 3-(2-furyl)propenal are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 89

3-[2-(3,4-dimethoxyphenyl)ethyl]-5-[(5-methyl(2-furyl))methylene]-2-thioxo-1,3-thiazolidin-4-one

3-[2-(3,4-dimethoxyphenyl)ethyl]-2-thioxo-1,3-thiazolidin-4-one and 5-methylfuran-2-carbaldehyde are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 90

5-{[5-(5-chloro-2-methylphenyl)(2-furyl)]methylene}-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one

Commercially available compound.

Example 91

3-prop-2-enyl-2-thioxo-5-({5-[3-(trifluoromethyl)phenyl](2-furyl)}methylene)-1,3-thiazolidin-4-one

Commercially available compound.

Example 92

3-{5-[(4-oxo-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzoic acid

Commercially available compound.

Example 93

5-{[5-(2-chlorophenyl)(2-furyl)]methylene}-3-(oxolan-2-ylmethyl)-2-thioxo-1,3-thiazolidin-4-one

Commercially available compound.

Example 94

3-(3-methoxypropyl)-5-{[5-(2-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one

Commercially available compound.

Example 95

5-[(3-methyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]thiophene-2-carbonitrile

N-methylrhodanine (94 mg, 0.64mmol) is combined with 1.33mL of the product from Example 55 (containing 0.64mmol of 5-Cyanothiophene-2-carboxaldehyde) and 1-methylpiperazine (0.02mL, 0.18mmol) and heated at 75 degrees for 38. hours under argon while stirring. The product is precipitated with 50mL water, washed with 120mL water and 20mL diethyl ether, and dried in vacuo. Yield: 93 mg, 54%. Optionally,further purification is carried out with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 96

3-ethyl-5-{[5-(hydroxymethyl)(2-thienyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one

The product from Example 44 and N-ethylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 97

3-ethyl-5-({5-[(methylsulfonyl)methyl](2-thienyl)}methylene)-2-thioxo-1,3-thiazolidin-4-one

The product from Example 45 and N-ethylrhodanine are combined using the procedure in Example 99 to produce the title compound.

Example 98

2-{5-[(3-methyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-thienyl}acetic acid

The product from Example 42 and N-methylrhodanine are combined using the procedure in Example 99 to produce the title compound.

Example 99

2-{5-[(3-ethyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-thienyl}acetic acid

The product from Example 42 (21mg, 0.12mmol), N-ethylrhodanine (125mg, 0.77mL), 1-methylpiperazine (0.02mL, 0.179695mL) and 2-ethoxyethanol (2mL) are stirred together under argon for 14 hours at 70°C. After removing solvent, 1mL EtOH is added and the product is eluted through a short silica gel column with hexane. The solvent is stripped *in vacuo* and the product is purified with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 100

3-(prop-2-enyl)-5-[(methylsulfonyl)methyl](2-thienyl)methylene-2-thioxo-1,3-thiazolidin-4-one

The product from Example 45 and N-allylrhodanine are combined using the procedure in Example 99 to produce the title compound.

Example 101

N-({5-[(3-ethyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-thienyl}methyl)acetamide

The product from Example 43 and N-ethylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 102

5-{[5-(aminomethyl)(2-thienyl)]methylene}-3-ethyl-2-thioxo-1,3-thiazolidin-4-one

The product from Example 56 and N-ethylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 103

3-ethyl-5-{[5-((hydroxyimino)methyl)(2-thienyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one

The product from Example 85 (58.1mg, 0.21mmol) is combined with hydroxylamine hydrochloride (63.2mg, 0.91mmol) in pyridine (1mL) and stirred under argon at 25°C for 48 hours. 125mL water and 75mL hexanes are added and filtered. The residue is dried *in vacuo* to yield 34mg (56%) of the title compound as a mixture of E and Z isomers.

Example 104

3-methyl-5-({5-[(methylsulfonyl)methyl](2-thienyl)}methylene)-2-thioxo-1,3-thiazolidin-4-one

The product from Example 45 and N-methylrhodanine are combined using the procedure in Example 99 to produce the title compound.

Example 105

3-ethyl-5-[(5-(2-thienyl)(2-thienyl))methylene]-2-thioxo-1,3-thiazolidin-4-one

5-(2-thienyl)thiophene-2-carbaldehyde and N-ethylrhodanine are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 106

3-prop-2-enyl-5-[(5-(2-thienyl)(2-thienyl))methylene]-2-thioxo-1,3-thiazolidin-4-one

5-(2-thienyl)thiophene-2-carbaldehyde and N-allylrhodanine are combined using the protocol in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate)to yield the title compound.

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 107

5-[(3-methyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]thiophene-2-carbonitrile

The product of Example 55 and N-methylrhodanine were combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate).

Optionally, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 108

5-[(3-ethyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]thiophene-2-carbonitrile

N-ethylrhodanine (94 mg, 0.64mmol) is combined with 1.33mL of the product from Example 55 (containing 0.64mmol of 5-Cyanothiophene-2-carboxaldehyde) and 1-methylpiperazine (0.02mL, 0.18mmol) and heated at 75°C for 38 hours. The product is precipitated with 50mL water, washed with 120mL water and 20mL diethyl ether, and dried *in vacuo*. Yield: 52 mg, 29%.

Optionally, further purification is carried out with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 109

5-[(4-oxo-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]thiophene-2-carbonitrile

N-allylrhodanine (111mg, 0.61mmol) is combined with 1.33mL of the product from Example 55 (containing 0.64mmol of 5-Cyanothiophene-2-carboxaldehyde) and 1-methylpiperazine (0.02mL, 0.18mmol) and heated at 75°C for 38 hours. The product is combined with ether and water (50mL each) and the water layer is extracted with two additional portions of ether. The organic phases are combined and washed with dilute hydrochloric acid, water and saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and stripped of solvent.

Optionally, further purification is carried out with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid

Example 110

3-cyclopentyl-N-[4-oxo-5-({5-[4-(phenylmethoxy)phenyl](2-furyl)}methylene)-2-thioxo(1,3-thiazolidin-3-yl)]propanamide

The product from Example 47 and the product from Example 48 are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate), and instead of precipitation, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 111

(4-methylphenyl)-N-[4-oxo-5-({5-[4-(phenylmethoxy)phenyl](2-furyl)}methylene)-2-thioxo(1,3-thiazolidin-3-yl)]carboxamide

The product from Example 47 and the product from Example 51 are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate), and instead of precipitation, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 112

3-cyclopentyl-N-(4-oxo-5-{[5-(3-phenylphenyl)(2-furyl)]methylene}-2-thioxo(1,3-thiazolidin-3-yl))propanamide

The product from Example 53 and the product from Example 48 are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate), and instead of precipitation, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 113

N-{2-[5-({2,4-dioxo-3-[2-(phenylcarbonylamino)ethyl]-1,3-thiazolidin-5-ylidene}methyl)-2-furyl]phenyl}acetamide

The product from Example 54 and 3-[2-(phenylcarbonylamino)ethyl]-1,3-thiazolidine-2,4-dione are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate), and instead of precipitation, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 114

N-{5-[(5-naphthyl(2-furyl))methylene]-4-oxo-2-thioxo-1,3-thiazolidin-3-yl}hexanamide

The product from Example 49 and 5-(1-naphthyl)furan-2-carbaldehyde are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate), and instead of precipitation, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 115

cyclohexyl-N-{5-[(5-naphthyl(2-furyl))methylene]-4-oxo-2-thioxo(1,3-thiazolidin-3-yl)}carboxamide

The product from Example 50 and 5-(1-naphthyl)furan-2-carbaldehyde are combined to yield the title compound using the procedure in Example 4, with the exception that, if necessary to dissolve the precursors, additional solvent is added (1:1 acetic acid/dimethylacetamide containing 0.5M sodium acetate), and instead of precipitation, purification with reverse phase HPLC on octadecylsilica is carried out using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid.

Example 116

N-(5-{[5-(aminomethyl)(2-thienyl)]methylene}-4-oxo-2-thioxo(1,3-thiazolidin-3-yl))cyclohexylcarboxamide

The following Example describes the obtainment of compounds deemed useful according to the present invention which will then be screened in a preliminary TNF/TNF receptor binding assay (see Example 118):

Example 117

The following compounds which fall withing the scope of the present invention are obtained commercially from various well-known sources:

3-phenyl-5-[(5-phenyl(2-furyl))methylene]-2-thioxo-1,3-thiazolidin-4-one,

3-[2-(3,4-dimethoxyphenyl)ethyl]-5-[(2,3-dimethoxyphenyl)methylene]-2-thioxo-1,3-thiazolidin-4-one,

5-[(2E)-3-(4-methoxyphenyl)prop-2-enylidene]-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,

5-((2E)-3-phenylprop-2-enylidene)-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,

1-(2-furylmethyl)-2-methylthio-4-[(5-nitro(2-thienyl))methylene]-2-imidazolin-5-one,

5-[(2,3-dimethoxyphenyl)methylene]-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,

5-[(4-methylphenyl)amino]-3-phenyl-2-thioxo-1,3-thiazolidin-4-one,

5-(indan-5-ylmethylene)-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one,

3-ethyl-5-[(2-hydroxy-3-methoxyphenyl)methylene]-2-thioxo-1,3-thiazolidin-4-one,

5-[(2-cyclohexylthiophenyl)methylene]-3-benzyl-2-thioxo-1,3-thiazolidin-4-one,

5-{[2-(2-furylmethylthio)-5-nitrophenyl]methylene}-3-benzyl-2-thioxo-1,3-thiazolidin-4-one,

1-[2-(3-chlorophenoxy)ethyl]-2-methylthio-4-[(4-nitrophenyl)methylene]-2-imidazolin-5-one,

1-(2-furylmethyl)-4-[(2-hydroxyphenyl)methylene]-2-methylthio-2-imidazolin-5-one,

5-[(5-methyl(2-furyl))methylene]-3-phenyl-1,3-thiazolidine-2,4-dione,

3-ethyl-5-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one,

3-(4-chlorophenethyl)-5-[(5-methyl-2-furyl)methylene]-2-thioxo-1,3-thiazolan-4-one,

5-{[5-(5-chloro-2-methylphenyl)(2-furyl)]methylene}-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one,

3-prop-2-enyl-2-thioxo-5-({5-[3-(trifluoromethyl)phenyl](2-furyl)}methylene)-1,3-thiazolidin-4-one,

3-{5-[(4-oxo-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzoic acid,

5-{[5-(2-chlorophenyl)(2-furyl)]methylene}-3-(oxolan-2-ylmethyl)-2-thioxo-1,3-thiazolidin-4-one,

3-(3-methoxypropyl)-5-{[5-(2-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one

These compound are screened in a preliminary TNF/TNF receptor binding assay (see Example 118) to demonstrate their suitability for use as specific inhibitors of TNF-dependent NF-κB activation signaled by certain members of the TNF receptor superfamily for the prophylaxis and treatment of inflammatory diseases.

Example 118

The compounds synthesized in Examples 1-116, and those obtained as described in Example 117 are screened for their ability to bind to TNF receptor, in order to identify candidates with potential TNF inhibitory activity, generally according to the following protocol:

Preparation of [Eu^{3+}]TNF-α

Eu^{3+}-chelate of N^1-(p-isothiocyanatobenzyl)-diethylenetriamine-N^1, N^2, N^3, N^3-tetraacetic acid (DTTA; EG&G Wallac, Gathersburg, MD) is used to prepare [Eu^{3+}]TNF-α. 100μg lyophilized TNF-α is resuspended in 100μl of labeling buffer (50mM $NaHCO_3$, pH 8.5, containing 0.9% NaCl). [Eu^{3+}]-DTTA (50 μg) is then added to TNF-α in the labeling buffer. The reaction is carried out at 4°C for 48 hours. The sample is then diluted 2-fold into 50mM Tris buffer (pH 7.8) containing 0.9% NaCl and 0.05% NaN_3, and dialyzed against 1 liter 50mM Tris buffer to remove free Eu^{3+}-DTTA label. The protein concentration is determined by the Bradford method (Bradford, 1976) and the specific activity is calculated using a europium standard solution (Wallac).

Ligand binding assay

The ligand binding assay is performed as follows: 96-well plates are coated with 10ng of TNF receptor in 50mM $NaHCO_3$ (pH 9.6) overnight at 4°C. Plates are then blocked with 0.2% BSA in PBS buffer, washed once with binding buffer (0.2%BSA/PBS/0.1% Tween-20), and incubated with Eu^{3+}-labeled TNF-α and the selected title compound from Examples 1-20 for one and a half-hours at room temperature. The plates are then washed three times with DELFIA Wash Solution (Wallac) and 100μl of DELFIA Enhancement Solution (Wallace) is added. The plate is placed on a plate shaker for 10 min before reading using a Victor Flurometer 1420 (Wallac). The europium counting protocol is used with a 320-nm excitation pulse at a frequency of 1000 s^{-1} and detection at 615 nm (emission wavelength). Fluorescence signal is measured after a delay of 400 μsec between each excitation pulse. Non-specific binding is defined using TNF-α with 500-fold excess of [Eu^{3+}]TNF-α. Each experimental point is carried out in duplicate.

Determination of Receptor Binding

The data ligand receptor interaction data is analyzed using Prizm (GraphPad Software). Ligand binding data are analyzed by non-linear least-square regression. Saturation data are fitted to a rectangular hyperbola model and competition data are fitted to a sigmoidal curve with a variable slope. Inhibition constants (Ki) are determined from IC_{50} values using the Chang-Prusoff equation (Cheng & Prusoff, 1973). In analyzing the data generated from testing the compounds of Examples 1-20, it is determined that each compound is capable of binding the TNF receptor R1. Thus, each compound serves as a candidate for analysis in an assay of biological activity.

Example 119

The compounds synthesized in Examples 1-20 and identified in Example 116 and 117 as being able to bind to TNF receptor are tested for their TNF inhibitory activity in a biological assay, generally according to the following protocol:

MRC-5 cells (available as ATCC CCL-171 from the American Type Culture Collection) are incubated at a density of $5x10^4$ cells per chamber in culture medium (Eagle's MEM with 2mM L-glutamine and Earle's BSS adjusted to contain 1.5g/L sodium bicarbonate, 0.1mM non-essential amino acid, 1.0mM sodium pyruvate, 10% fetal bovine serum (FBS)) on Fisher culture slides overnight at 37°C and 5% CO_2.

The next day, the medium is removed and Earle's MEM without FBS is added to each chamber. 0.1nM TNF-α is then added to each, as well as 100μM of the test compound (negative control is no TNF-α, positive control is 0.1nM TNF-α with no test compound added). The slides are placed in a 37°C incubator for 15 minutes.

The chambers are washed twice with PBS. The cells are fixed by incubating in ice cold MeOH for five minutes and allowed to air dry. The cells are then washed three times with PBS. The specimen is incubated with 10% FBS in PBS for 20 minutes to suppress non-specific binding of IgG, then washed once with PBS.

The chambers are then incubated with goat anti-human NF-κB p65 (Santa Cruz Biotechnology, Inc.) at 1:500 dilution in PBS with 1.5% FBS for 60 minutes. The chambers are then washed three times with PBS for 5 minutes each, and incubated for 45 minutes in a dark chamber with fluorescein goat anti-rabbit IgG (Santa Cruz Biotechnology, Inc.) diluted 1:200 in PBS with 1.5% FBS. After a final wash three times with PBS, a coverslip is mounted with SlowFade™ AntiFade (Molecular Probes).

In order to score the results, the chambers are examined using a fluorescence microscope with an appropriate filter. At least 500 cells are counted per chamber and the location of the fluorescence is noted as either nuclear only, nuclear and cytoplasmic, or cytoplasmic only. In accordance with this protocol, it is demonstrated that each of the compounds from Examples 1-20 posses TNF inhibitory activity to varying degrees.

Thus, the following new compounds are proven to be useful compounds for preventing or treating inflammatory diseases by inhibiting tumor necrosis factor activity:

5-(5-methylfuran-2-ylmethylene)-2-thioxo-3-methyl-thiazolidin-4-one,
5-(5-methylfuran-2-ylmethylene)-2-thioxo-3-allyl-thiazolidin-4-one,
5-(thiazol-2-ylmethylene)-2-thioxo-3-allyl-thiazolidin-4-one,
5-((3-phenoxy)thiophen-2-ylmethylene)-2-thioxo-3-ethyl-thiazolidin-4-one,
5-(5-(2-nitrophenyl)furan-2-ylmethylene)-2-thioxo-3-ethyl-thiazolidin-4-one,
5-(2,3,4-trimethoxy-benzylidene)-2-thioxo-3-ethyl-thiazolidin-4-one,
5-(5-(2-nitrophenyl)-2-furan2-ylmethylene)-2-thioxo-3-allyl-thiazolidin-4-one,
5-(5-(2-nitrophenyl)-2-furan2-ylmethylene)-thiazolidin-2,4-dione,
6-(5-(5-(2-nitrophenyl)-2-furanylidene)-4-oxo-2-thioxo-thiazolidin-3-yl)-hexanoic acid isopropyl ester,
5-(5-(2-chlorophenyl)furan-2-ylmethylene))-2-thioxo-3-ethyl-thiazolidin-4-one,
5-(5-(2-trifluoromethyl)furan-2-ylmethylene))-2-thioxo-3-ethyl-thiazolidin-4-one,
5-(5-(2-methoxycarbonylthiophen-3-yl)furan-2-ylmethylene))-2-thioxo-3-ethyl-thiazolidin-4-one,
5-(2-(furan-2-yl)eth-1-enylmethylene))-2-thioxo-3-ethyl-thiazolidin-4-one,
5-(3-(4-methoxyphenoxy)-benzylidene)-2-thioxo-3-ethyl-thiazolidin-4-one,
3-(2-furylmethyl)-5-{[5-(2-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one,
5-(2-methyl-3-phenylprop-2-enylidene)-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,
3-ethyl-5-{[3-(phenylmethoxy)phenyl]methylene}-2-thioxo-1,3-thiazolidin-4-one,
3-ethyl-5-{[5-(3-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one,
5-{[3,5-bis(tert-butyl)-4-hydroxyphenyl]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one,
5-({3-[4-(tert-butyl)phenoxy]phenyl}methylene)-3-methyl-2-thioxo-1,3-thiazolidin-4-one,
3-ethyl-5-(1,3-thiazol-2-ylmethylene)-2-thioxo-1,3-thiazolidin-4-one,
5-(2-methyl-3-phenylprop-2-enylidene)-3-methyl-2-thioxo-1,3-thiazolidin-4-one,

3-ethyl-5-{[3-(2-hydroxyethoxy)phenyl]methylene}-2-thioxo-1,3-thiazolidin-4-one,
3-methyl-5-{[3-(4-methylphenoxy)phenyl]methylene}-2-thioxo-1,3-thiazolidin-4-one,
3-methyl-5-{[5-(3-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one,
5-(5-{2-nitrophenylfuran-2-ylmethylene})-2-thioxo-3-methyl-thiazolidin-4-one,
3-ethyl-5-{[3-(4-methylphenoxy)phenyl]methylene}-2-thioxo-1,3-thiazolidin-4-one,
5-{[3-(4-methoxyphenoxy)phenyl]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one,
5-({3-[4-methylphenoxy]phenyl}methylene)-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one,
5-{[3,5-bis(tert-butyl)-4-hydroxyphenyl]methylene}-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,
5-({3-[4-methoxyphenoxy]phenyl}methylene)-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one,
5-({3-[4-(tert-butyl)phenoxy]phenyl}methylene)-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,
3-ethyl-5-{[5-(2-trifluoromethoxyphenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one,
5-({3-[4-(tert-butyl)phenoxy]phenyl}methylene)-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one,
5-({2,5-dimethyl-1-[3-(trifluoromethyl)phenyl]pyrrol-3-yl}methylene)-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,
3-(3-hydroxyphenyl)-5-{[5-(2-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one,
3-(4-ethoxyphenyl)-5-{[5-(2-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one,
5-{[3,5-bis(phenylmethoxy)phenyl]methylene}-3-ethyl-2-thioxo-1,3-thiazolidin-4-one-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one,
3-methyl-5-(1,3-thiazol-2-ylmethylene)-2-thioxo-1,3-thiazolidin-4-one,
5-[(5-methyl(2-furyl))methylene]-3-ethyl-2-thioxo-1,3-thiazolidin-4-one, and
N-(5-{[5-(aminomethyl)(2-thienyl)]methylene}-4-oxo-2-thioxo(1,3-thiazolidin-3-yl))cyclohexylcarboxamide.

In addition, the following commercially-available compounds are proven to have a new use as compounds for preventing or treating inflammatory diseases by inhibiting tumor necrosis factor activity:

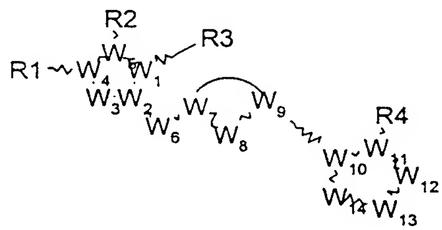
3-phenyl-5-[(5-phenyl(2-furyl))methylene]-2-thioxo-1,3-thiazolidin-4-one,
3-[2-(3,4-dimethoxyphenyl)ethyl]-5-[(2,3-dimethoxyphenyl)methylene]-2-thioxo-1,3-thiazolidin-4-one,
5-[(2E)-3-(4-methoxyphenyl)prop-2-enylidene]-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,
5-((2E)-3-phenylprop-2-enylidene)-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,
1-(2-furylmethyl)-2-methylthio-4-[(5-nitro(2-thienyl))methylene]-2-imidazolin-5-one,
5-[(2,3-dimethoxyphenyl)methylene]-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,
5-[(4-methylphenyl)amino]-3-phenyl-2-thioxo-1,3-thiazolidin-4-one,
5-(indan-5-ylmethylene)-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one,
3-ethyl-5-[(2-hydroxy-3-methoxyphenyl)methylene]-2-thioxo-1,3-thiazolidin-4-one,
5-[(2-cyclohexylthiophenyl)methylene]-3-benzyl-2-thioxo-1,3-thiazolidin-4-one,
5-{[2-(2-furylmethylthio)-5-nitrophenyl]methylene}-3-benzyl-2-thioxo-1,3-thiazolidin-4-one,
1-[2-(3-chlorophenoxy)ethyl]-2-methylthio-4-[(4-nitrophenyl)methylene]-2-imidazolin-5-one,
1-(2-furylmethyl)-4-[(2-hydroxyphenyl)methylene]-2-methylthio-2-imidazolin-5-one,
5-[(5-methyl(2-furyl))methylene]-3-phenyl-1,3-thiazolidine-2,4-dione, and
3-ethyl-5-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one,

All patents and patent applications cited in this specification are hereby incorporated by reference as if they had been specifically and individually indicated to be incorporated by reference.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity and understanding, it will be apparent to those of ordinary skill in the art in light of the disclosure that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

Claims:

1. A compound for treating inflammatory diseases by inhibiting tumor necrosis factor activity comprising a compound of the formula:



wherein

W1W2W3W4W5 is an alicyclic, heterocyclic, or heteroaromatic ring, with the provisos that

the ring is not fused with any other ring, and

the ring is not a pyrrazole, dihydropyrrazole, or tetrahydropyrrazole derivative;

The ring containing W7, W8 and W9 is alicyclic, heterocyclic, aromatic or heteroaromatic;

The W10-W14 ring is alicyclic, heterocyclic, or heteroaromatic;

The bonds between any two adjacent W atoms can be either single, double or aromatic (valence permitting);

W6 is not part of a ring;

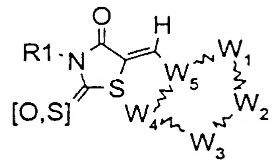
The W9-W10 bond is not part of a ring;

W2, W7, W9, and W10 are each independently either N, C, or C with one substituent group (valence permitting);

W1, W4, W5, and W11 are each independently either SOx (where x is 1 or 2), N, C, or C with one substituent group (valence permitting); and

W3, W6, W8, W12, W13, and W14 are each independently either O, S, SO, SO_2, N, C, C with one substituent group (either single or double bonded), N with one substituent group (single bonded), or PO(OR).

2. A compound for treating inflammatory diseases by inhibiting tumor necrosis factor activity comprising a compound of the formula:



wherein

W1W2W3W4W5 is an aliphatic, heterocyclic, or heteroaromatic ring, with the provisos that:

If W1 is CW6R2 or NW7R3, where W6 is CR4R5, CR6, O, S, NR7, SO, SO_2, CO, C=NOR8, or C=NNR9R10, and W7 is CR4R5, CR6, O, NR7, SO, SO_2, CO, C=NOR8, or C=NNR9R10, then W1 is not at a ring bridgehead, and

If R2 and R3 are independently any alicyclic, heterocyclic, aromatic, or heteroaromatic ring structure, then

W2 is O, S, NR11, CR12R13, CR14, SO, or SO_2, (valence permitting),

W3 is O, S, NR15, CR16R17, CR18, SO, or SO_2, (valence permitting),

W4 is O, S, NR19, CR20R21, CR22, SO, or SO_2, (valence permitting), and

W5 is N, C, or CR36 (valence permitting)

If W2 is CR23 or NR24 where R23 or R24 is a five membered ring (alicyclic, heterocyclic, or heteroaromatic), then

W1 is O, S, NR25, CR26R27, CR28, SO, or SO_2, (valence permitting),

W3 is O, S, NR29, CR30R31, CR32, SO, or SO_2, (valence permitting),

W4 is O, S, NR33, CR34R35, CR36, SO, or SO_2, (valence permitting),

W5 is N, C, or CR37 (valence permitting),

If the ring W1W2W3W4W5 is neither 3-oxotetrahydrothiophene nor furan, or if the ring W1W2W3W4W5 is furan and R1 is not any of the groups in Exhibit A, then

W2 can be CR23 or NR24 where R23 or R24 is a six membered ring (alicyclic, heterocyclic, aromatic or heteroaromatic);

in addition,

W1 is O, S, NR25, CR26R27, CR28, SO, or SO_2, (valence permitting),

W3 is O, S, NR29, CR30R31, CR32, SO, or SO_2, (valence permitting),

W4 is O, S, NR33, CR34R35, CR36, SO, or SO_2, (valence permitting),

W5 is N, C, or CR37 (valence permitting),

R1 is independently H, heterocyclic, aromatic, heteroaromatic, small alkyl or cycloalkyl, optionally substituted with OH, O-alkyl, S-alkyl, hydroxy alkoxy, $CONH_2$, CONH-alkyl, OCF_3, CON-dialkyl, halo, CF_3, sulfonamide, phosphonamide, phosphonate ester, SO-alkyl, SO_2-alkyl, O-aryl, S-aryl, SO-aryl, SO_2-aryl, COO-alkyl, CONH-aryl, acyloxy, acylamino, alkylsulfonylamino, or arylsulfonylamino;

R3, R7 through R11, R15, R19, R24, R25, R29, R33 are each independently, H, heterocyclic, aromatic, heteroaromatic, small alkyl or cycloalkyl, optionally substituted with OH, O-alkyl, S-alkyl, $CONH_2$, CONH-alkyl, CON-dialkyl, F, CF_3, OCF_3, sulfonamide, phosphonamide, or phosphonate ester; and

R2, R4 through R6, R12 thorugh R14, R16 through R18, R20 through R23, R26 through R28, R30 through R32, and R34 through R37 are each independently H, halogen, OH, NH_2, or O-alkyl, OCF_3, O-cycloalkyl, heterocyclic, aromatic, heteroaromatic, small alkyl or cycloalkyl, optionally substituted with OH, O-alkyl, S-alkyl, SO-alkyl, SO_2-alkyl, $CONH_2$, CONH-alkyl, CON-dialkyl, F, CF_3, sulfonamide, phosphonamide, or phosphonate ester.

3. A compound according to claim 2 which is a compound selected from the group consisting of:

5-(5-methylfuran-2-ylmethylene)-2-thioxo-3-methyl-thiazolidin-4-one,

5-(5-methylfuran-2-ylmethylene)-2-thioxo-3-allyl-thiazolidin-4-one,

5-(thiazol-2-ylmethylene)-2-thioxo-3-allyl-thiazolidin-4-one,

5-((3-phenoxy)thiophen-2-ylmethylene)-2-thioxo-3-ethyl-thiazolidin-4-one,

5-(5-(2-nitrophenyl)furan-2-ylmethylene)-2-thioxo-3-ethyl-thiazolidin-4-one,

5-(2,3,4-trimethoxy-benzylidene)-2-thioxo-3-ethyl-thiazolidin-4-one,

5-(5-(2-nitrophenyl)-2-furan2-ylmethylene)-2-thioxo-3-allyl-thiazolidin-4-one,

5-(5-(2-nitrophenyl)-2-furan2-ylmethylene)-thiazolidin-2,4-dione,

6-(5-(5-(2-nitrophenyl)-2-furanylidene)-4-oxo-2-thioxo-thiazolidin-3-yl)-hexanoic acid isopropyl ester,

5-(5-(2-chlorophenyl)furan-2-ylmethylene))-2-thioxo-3-ethyl-thiazolidin-4-one,

5-(5-(2-trifluoromethyl)furan-2-ylmethylene))-2-thioxo-3-ethyl-thiazolidin-4-one,

5-(5-(2-methoxycarbonylthiophen-3-yl)furan-2-ylmethylene))-2-thioxo-3-ethyl-thiazolidin-4-one,

5-(2-(furan-2-yl)eth-1-enylmethylene))-2-thioxo-3-ethyl-thiazolidin-4-one,

5-(3-(4-methoxyphenoxy)-benzylidene)-2-thioxo-3-ethyl-thiazolidin-4-one,

3-(2-furylmethyl)-5-{[5-(2-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one,

5-(2-methyl-3-phenylprop-2-enylidene)-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,

3-ethyl-5-{[3-(phenylmethoxy)phenyl]methylene}-2-thioxo-1,3-thiazolidin-4-one,

3-ethyl-5-{[5-(3-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one,

5-{[3,5-bis(tert-butyl)-4-hydroxyphenyl]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one,

5-({3-[4-(tert-butyl)phenoxy]phenyl}methylene)-3-methyl-2-thioxo-1,3-thiazolidin-4-one,

3-ethyl-5-(1,3-thiazol-2-ylmethylene)-2-thioxo-1,3-thiazolidin-4-one,

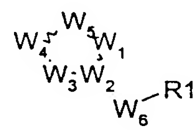
5-(2-methyl-3-phenylprop-2-enylidene)-3-methyl-2-thioxo-1,3-thiazolidin-4-one,

3-ethyl-5-{[3-(2-hydroxyethoxy)phenyl]methylene}-2-thioxo-1,3-thiazolidin-4-one,

3-methyl-5-{[3-(4-methylphenoxy)phenyl]methylene}-2-thioxo-1,3-thiazolidin-4-one,
3-methyl-5-{[5-(3-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one,
5-(5-{2-nitrophenylfuran-2-ylmethylene})-2-thioxo-3-methyl-thiazolidin-4-one,
3-ethyl-5-{[3-(4-methylphenoxy)phenyl]methylene}-2-thioxo-1,3-thiazolidin-4-one,
5-{[3-(4-methoxyphenoxy)phenyl]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one,
5-({3-[4-methylphenoxy]phenyl}methylene)-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one,
5-{[3,5-bis(tert-butyl)-4-hydroxyphenyl]methylene}-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,
5-({3-[4-methoxyphenoxy]phenyl}methylene)-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one,
5-({3-[4-(tert-butyl)phenoxy]phenyl}methylene)-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,
3-ethyl-5-{[5-(2-trifluoromethoxyphenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one,
5-({3-[4-(tert-butyl)phenoxy]phenyl}methylene)-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one,
5-({2,5-dimethyl-1-[3-(trifluoromethyl)phenyl]pyrrol-3-yl}methylene)-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,
3-(3-hydroxyphenyl)-5-{[5-(2-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one,
3-(4-ethoxyphenyl)-5-{[5-(2-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one,
5-{[3,5-bis(phenylmethoxy)phenyl]methylene}-3-ethyl-2-thioxo-1,3-thiazolidin-4-one-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one,
3-methyl-5-(1,3-thiazol-2-ylmethylene)-2-thioxo-1,3-thiazolidin-4-one, and
5-[(5-methyl(2-furyl))methylene]-3-ethyl-2-thioxo-1,3-thiazolidin-4-one.

4. A method for preventing or treating inflammatory diseases by inhibiting tumor necrosis factor activity comprising

administering a compound of the formula:



wherein

W1W2W3W4W5 is an alicyclic, heterocyclic or heteroaromatic ring, wherein

W1 is O, S, NR2, CHR9, CR10, or P=O(OR43) (valence permitting);

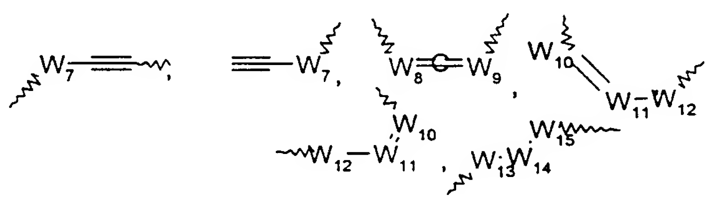
W2 is C or N (valence permitting);

W3 is C=O, C=S, C-X, CR11, NR12, SO, SO_2, P=O(OR44) (valence permitting);

W4 is CR4, NR13, C=S, CO, SO, S, SO_2, P=O(OR45) (valence permitting);

W5 is C=O, C=S, C-X, CR3, NR5, SO, SO_2, P=O(OR46) (valence permitting);

W6 is CR47, O, S, SO, SO_2, NR6, CR7R8, P=O(OR48) (valence permitting), or a group of the formula:



where all double bond stereochemistry can independently be either Z or E, and where the bonds from W2 to W6 and from W6 to R1 can be, independently, either single or double (valence permitting),

W7 is CR14R15, CO, C=NOR25 or C=NNR26R27;

W8 is CR16;

W9 is CR17;

W10 is N or CR18;

W11 is CH, N, CCH_3, CF, CCH_2CH_3, or CCl;

W12 is O, S, NR19 or CR20R21;

W13 is CR22R23, O, S, NR24, SO_2, SO, CO, C=NOR28, or C=NNR29R30;

W14 is CR31R32, O, S, NR33, SO_2, SO, CO, C=NOR34, or C=NNR35R36;

W15 is CR37R38, O, S, NR39, SO_2, SO, CO, C=NOR40, C=NNR41R42;

Where

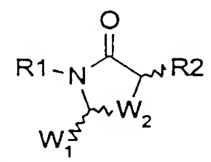
R1 is any 5- or 6- membered alicyclic, heterocyclic, aromatic, or heteroaromatic ring, unsubstituted or substituted with alkyl, cycloalkyl, branched alkyl, halogen, trifluoroalkyl, alkoxy, aryloxy or benzoyloxy (unsubstituted or substituted with nitro, alkyl, branched alkyl or alkoxy), amide, ester, trifluoromethyl, nitro, NR7R8 (where R7 is hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, alkyl, cycloalkyl, heterocylic, alicyclic and R8 is acyl, alkoxyacyl, carbamoyl, N-alkylcarbamoyl, alkoxycarbonyl, hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, alkyl, cycloalkyl, heterocylic, alicyclic), unsubstituted or substituted with a 5- or 6-membered ring attached directly or through O, NH, CH_2, S, NCHO, NCH_3, CO, CHOH, $CHCH_3$, or $C=CH_2$;

R2, R5, R6, R12, R13, R19, R24 through R30, R33 through R36, R39 through R46, R48 are each independently, H, heterocyclic, aromatic, heteroaromatic, allyl, alkenyl alkyl, alkenyl, small alkyl or cycloalkyl, optionally substituted with OH, O-alkyl, S-alkyl, $CONH_2$, CONH-alkyl, CON-dialkyl, NHCO-alkyl, NHCO-aryl, NHCO-heteroaryl, F, CF_3, sulfonamide, phosphonamide, or phosphonate ester; and

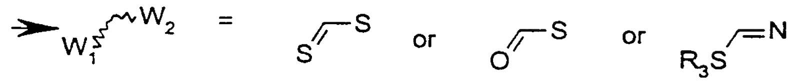
R3, R4, R7 through R11, R14 through R18, R20 through R23, R31, R32, R37, R38, R47 are each independently H, halogen, OH, NH_2, or O-alkyl, O-cycloalkyl, heterocyclic, aromatic, heteroaromatic, small alkyl or cycloalkyl, unsubstituted or substituted with OH, O-alkyl, S-alkyl, SO-alkyl, SO_2-alkyl, $CONH_2$, CONH-alkyl, CON-dialkyl, F, CF_3, OCF_3, sulfonamide, phosphonamide, or phosphonate ester; together with a pharmaceutically acceptable carrier to a patient in need of such treatment.

5. A method for preventing or treating inflammatory diseases by inhibiting tumor necrosis factor activity comprising

administering a compound of the formula:



Where

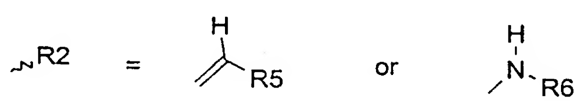


where R3 is H or short alkyl or cycloalkyl;

wherein

R1 is H, straight or branched alkyl (C1-C10) unsubstituted or substituted by:

COOR4 (where R4 is H, short alkyl, cycloalkyl, or branched alkyl), an aromatic or heteroaromatic ring, or by aryloxy; or alkenyl, or aromatic or heteroaromatic ring, unsubstituted or substituted by alkyl, hydroxy or alkoxy;



(wherein the bond from 5 membered ring to R2 is double for CHR5 and single for NHR6);

R5 is CR7=CHR8 with R7=H or small alkyl and R8=aryl or heteroaryl, unsubstituted or substituted by alkoxy; or aromatic or heteroaromatic or substituted by short alkyl;

or nitro; or alkoxy (including multiple alkoxy); or aryloxy or substituted by alkoxy or alkyl; or aromatic or heteroaromatic, unsubstituted or substituted by halo, trifluoromethyl, trifluoromethoxy, alkoxy, alkyl, COOR10 (where R10 is H, short alkyl, cycloalkyl, or branched alkyl) or fused to a 5 membered carboxyclic or

heterocyclic ring;

R6 is aromatic or heteroaromatic, unsubstituted or substituted by short alkyl; nitro; alkoxy (including multiple alkoxy); aryloxy unsubstituted or substituted by alkoxy or alkyl; aromatic or heteroaromatic, unsubstituted or substituted by halo, trifluoromethyl, trifluoromethoxy, alkoxy, alkyl, COOR11 (where R11 is H, short alkyl, cycloalkyl, or branched alkyl) or fused to a 5 membered carboxyclic or heterocyclic ring;

together with a pharmaceutically acceptable carrier to a patient in need of such treatment.

6. A method according to claim 5 which employs a compound selected from the group consisting of:

5-(5-methylfuran-2-ylmethylene)-2-thioxo-3-methyl-thiazolidin-4-one,

5-(5-methylfuran-2-ylmethylene)-2-thioxo-3-allyl-thiazolidin-4-one,

5-(thiazol-2-ylmethylene)-2-thioxo-3-allyl-thiazolidin-4-one,

5-((3-phenoxy)thiophen-2-ylmethylene)-2-thioxo-3-ethyl-thiazolidin-4-one,

5-(5-(2-nitrophenyl)furan-2-ylmethylene)-2-thioxo-3-ethyl-thiazolidin-4-one,

5-(2,3,4-trimethoxy-benzylidene)-2-thioxo-3-ethyl-thiazolidin-4-one,

5-(5-(2-nitrophenyl)-2-furan2-ylmethylene)-2-thioxo-3-allyl-thiazolidin-4-one,

5-(5-(2-nitrophenyl)-2-furan2-ylmethylene)-thiazolidin-2,4-dione,

6-(5-(5-(2-nitrophenyl)-2-furanylidene)-4-oxo-2-thioxo-thiazolidin-3-yl)-hexanoic acid isopropyl ester,

5-(5-(2-chlorophenyl)furan-2-ylmethylene))-2-thioxo-3-ethyl-thiazolidin-4-one,

5-(5-(2-trifluoromethyl)furan-2-ylmethylene))-2-thioxo-3-ethyl-thiazolidin-4-one,

5-(5-(2-methoxycarbonylthiophen-3-yl)furan-2-ylmethylene))-2-thioxo-3-ethyl-thiazolidin-4-one,

5-(2-(furan-2-yl)eth-1-enylmethylene))-2-thioxo-3-ethyl-thiazolidin-4-one,

5-(3-(4-methoxyphenoxy)-benzylidene)-2-thioxo-3-ethyl-thiazolidin-4-one,

3-(2-furylmethyl)-5-{[5-(2-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one,

5-(2-methyl-3-phenylprop-2-enylidene)-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,

3-ethyl-5-{[3-(phenylmethoxy)phenyl]methylene}-2-thioxo-1,3-thiazolidin-4-one,

3-ethyl-5-{[5-(3-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one,

5-{[3,5-bis(tert-butyl)-4-hydroxyphenyl]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one,

5-({3-[4-(tert-butyl)phenoxy]phenyl}methylene)-3-methyl-2-thioxo-1,3-thiazolidin-4-one,

3-ethyl-5-(1,3-thiazol-2-ylmethylene)-2-thioxo-1,3-thiazolidin-4-one,

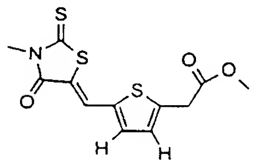
5-(2-methyl-3-phenylprop-2-enylidene)-3-methyl-2-thioxo-1,3-thiazolidin-4-one,

3-ethyl-5-{[3-(2-hydroxyethoxy)phenyl]methylene}-2-thioxo-1,3-thiazolidin-4-one,

3-methyl-5-{[3-(4-methylphenoxy)phenyl]methylene}-2-thioxo-1,3-thiazolidin-4-one,
3-methyl-5-{[5-(3-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one,
5-(5-{2-nitrophenylfuran-2-ylmethylene})-2-thioxo-3-methyl-thiazolidin-4-one,
3-ethyl-5-{[3-(4-methylphenoxy)phenyl]methylene}-2-thioxo-1,3-thiazolidin-4-one,
5-{[3-(4-methoxyphenoxy)phenyl]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one,
5-({3-[4-methylphenoxy]phenyl}methylene)-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one,
5-{[3,5-bis(tert-butyl)-4-hydroxyphenyl]methylene}-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,
5-({3-[4-methoxyphenoxy]phenyl}methylene)-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one,
5-({3-[4-(tert-butyl)phenoxy]phenyl}methylene)-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,
3-ethyl-5-{[5-(2-trifluoromethoxyphenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one,
5-({3-[4-(tert-butyl)phenoxy]phenyl}methylene)-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one,
5-({2,5-dimethyl-1-[3-(trifluoromethyl)phenyl]pyrrol-3-yl}methylene)-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,
3-(3-hydroxyphenyl)-5-{[5-(2-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one,
3-(4-ethoxyphenyl)-5-{[5-(2-nitrophenyl)(2-furyl)]methylene}-2-thioxo-1,3-thiazolidin-4-one,
5-{[3,5-bis(phenylmethoxy)phenyl]methylene}-3-ethyl-2-thioxo-1,3-thiazolidin-4-one-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one,
3-methyl-5-(1,3-thiazol-2-ylmethylene)-2-thioxo-1,3-thiazolidin-4-one,
5-[(5-methyl(2-furyl))methylene]-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,
3-phenyl-5-[(5-phenyl(2-furyl))methylene]-2-thioxo-1,3-thiazolidin-4-one,
3-[2-(3,4-dimethoxyphenyl)ethyl]-5-[(2,3-dimethoxyphenyl)methylene]-2-thioxo-1,3-thiazolidin-4-one,
5-[(2E)-3-(4-methoxyphenyl)prop-2-enylidene]-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,

5-((2E)-3-phenylprop-2-enylidene)-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,
1-(2-furylmethyl)-2-methylthio-4-[(5-nitro(2-thienyl))methylene]-2-imidazolin-5-one,
5-[(2,3-dimethoxyphenyl)methylene]-3-ethyl-2-thioxo-1,3-thiazolidin-4-one,
5-[(4-methylphenyl)amino]-3-phenyl-2-thioxo-1,3-thiazolidin-4-one,
5-(indan-5-ylmethylene)-3-prop-2-enyl-2-thioxo-1,3-thiazolidin-4-one,
3-ethyl-5-[(2-hydroxy-3-methoxyphenyl)methylene]-2-thioxo-1,3-thiazolidin-4-one,
5-[(2-cyclohexylthiophenyl)methylene]-3-benzyl-2-thioxo-1,3-thiazolidin-4-one,
5-{[2-(2-furylmethylthio)-5-nitrophenyl]methylene}-3-benzyl-2-thioxo-1,3-thiazolidin-4-one,
1-[2-(3-chlorophenoxy)ethyl]-2-methylthio-4-[(4-nitrophenyl)methylene]-2-imidazolin-5-one,
1-(2-furylmethyl)-4-[(2-hydroxyphenyl)methylene]-2-methylthio-2-imidazolin-5-one,
5-[(5-methyl(2-furyl))methylene]-3-phenyl-1,3-thiazolidine-2,4-dione, and
3-ethyl-5-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one.

structure



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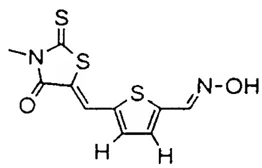

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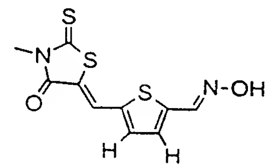

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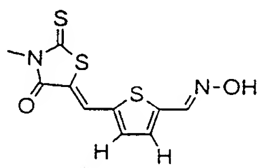

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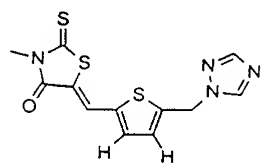

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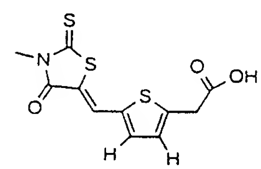
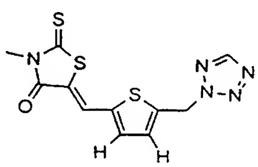


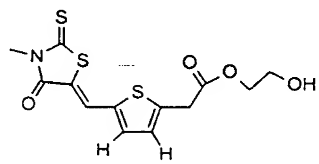
ID 6

structure



ID 7

structure



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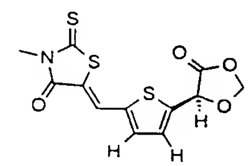

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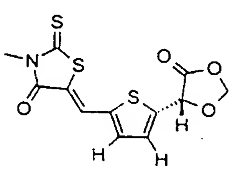

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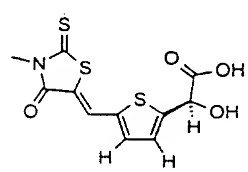

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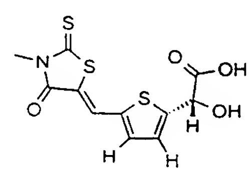

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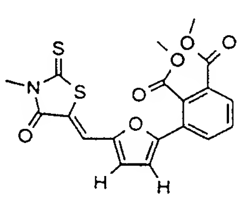

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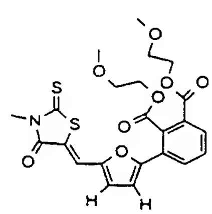

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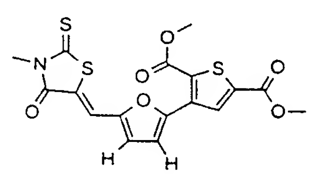

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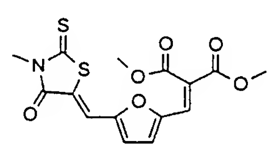	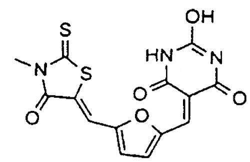	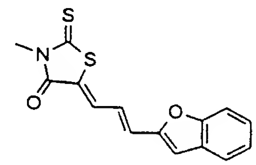
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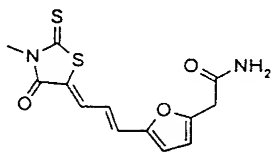	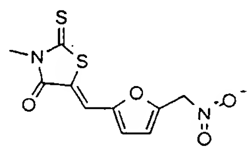	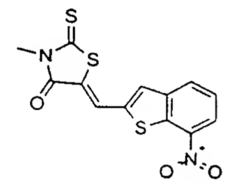
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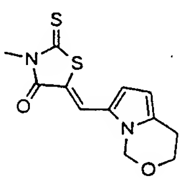	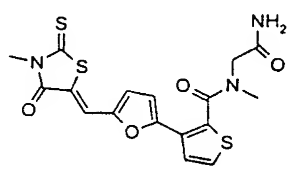	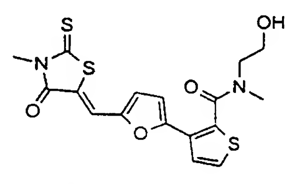
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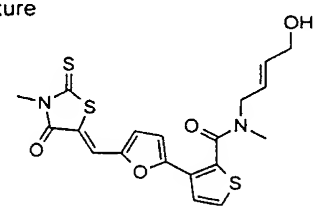	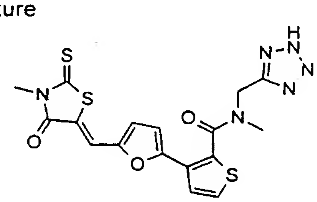	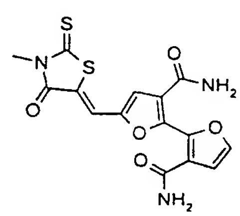
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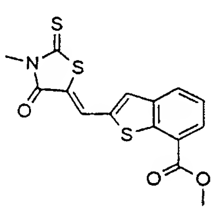	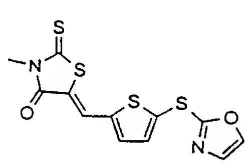	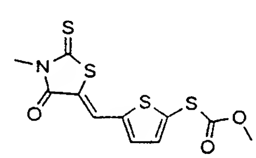
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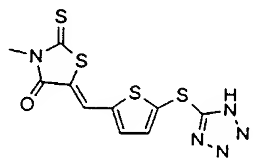

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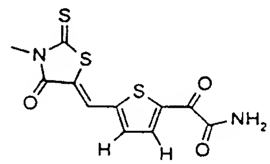

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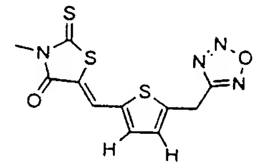

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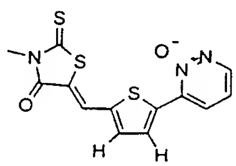

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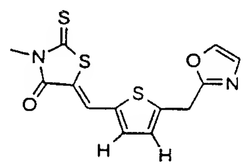

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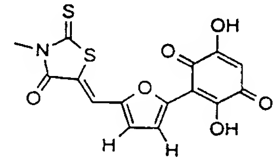

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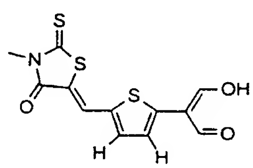

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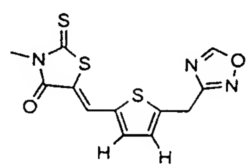

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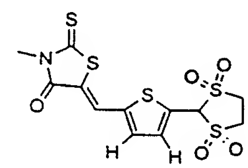

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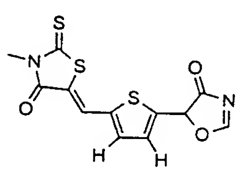

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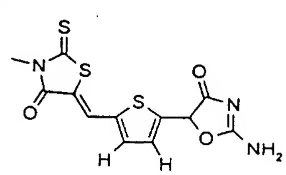

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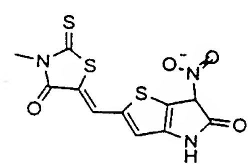

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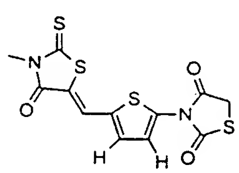

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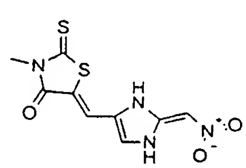

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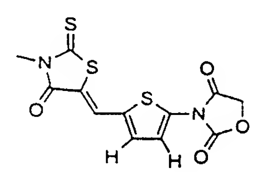

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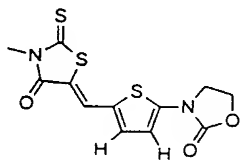

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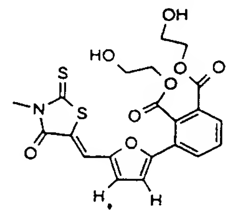

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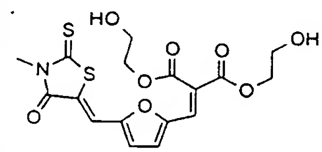

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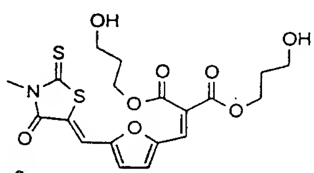

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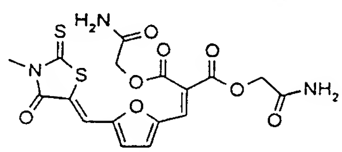

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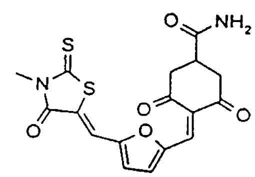

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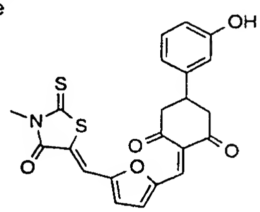

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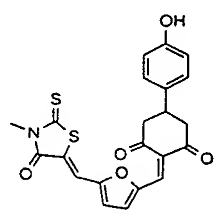

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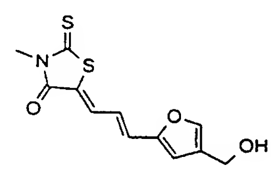

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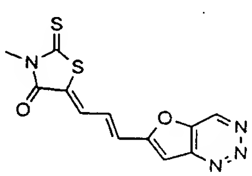

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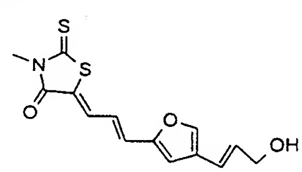

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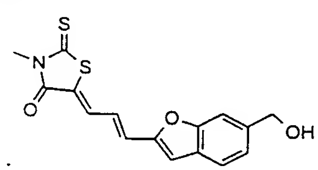

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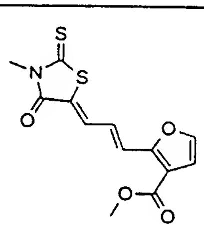

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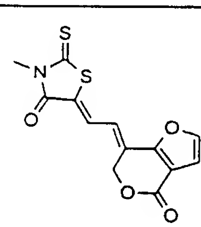

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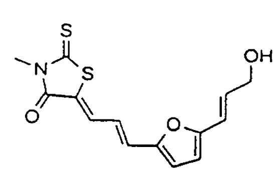

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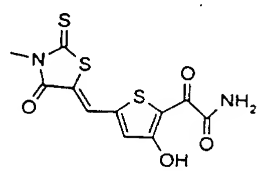

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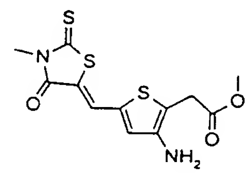

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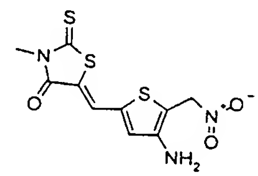

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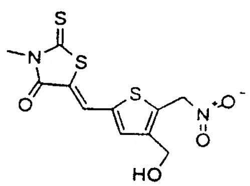

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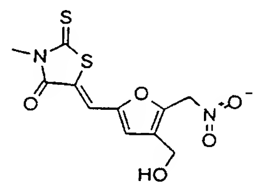

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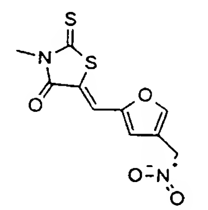

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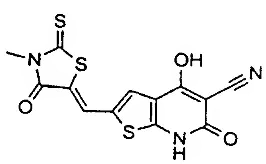

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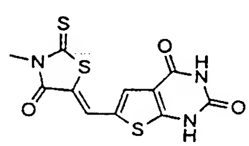

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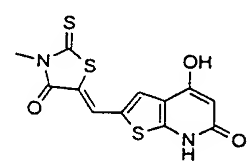

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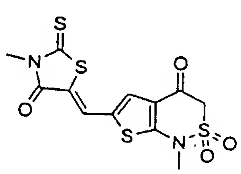

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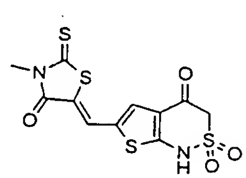

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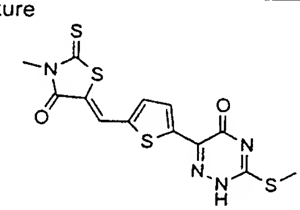

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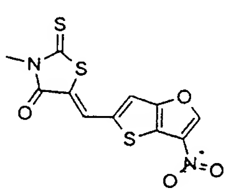

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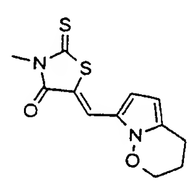

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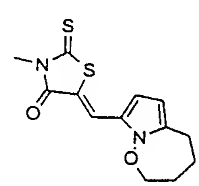

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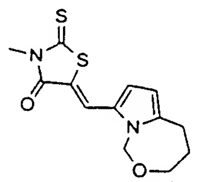

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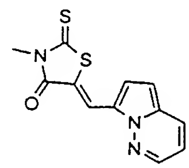

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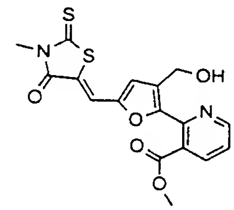

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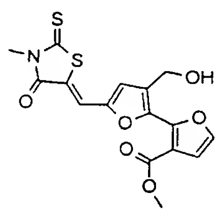

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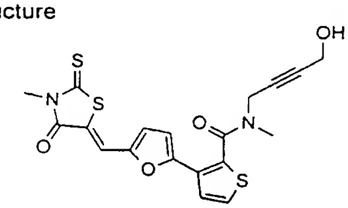

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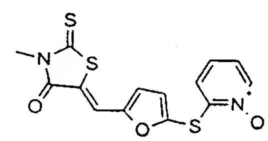

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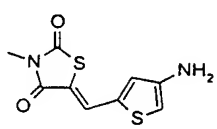

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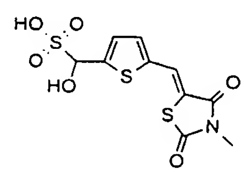

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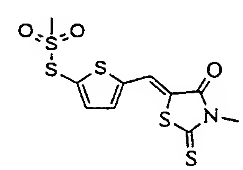

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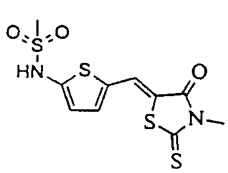

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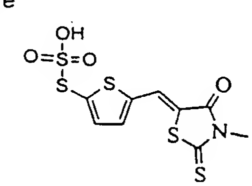

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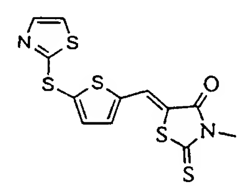

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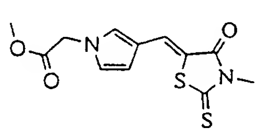

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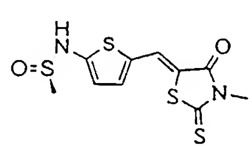

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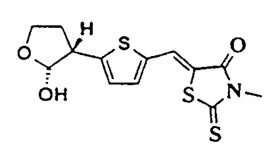

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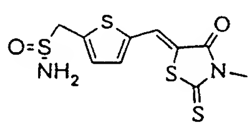

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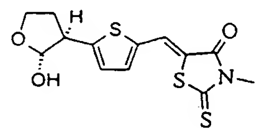

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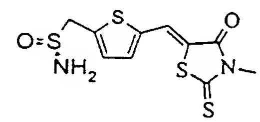

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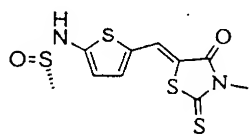

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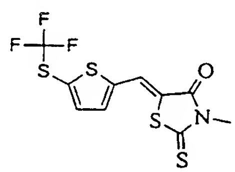

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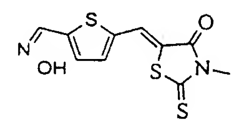

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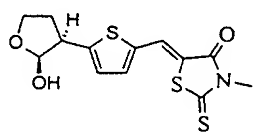

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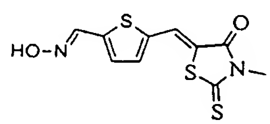

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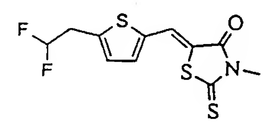

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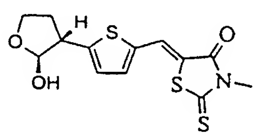

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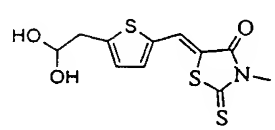

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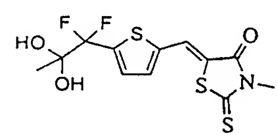

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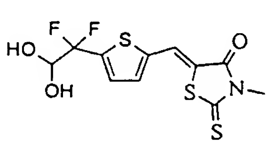

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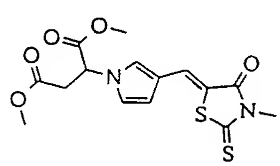

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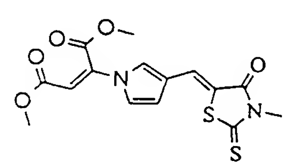

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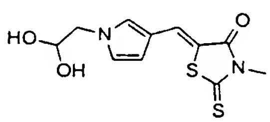

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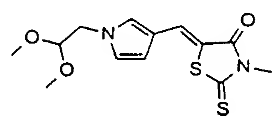

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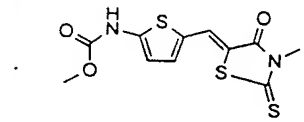

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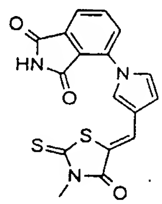

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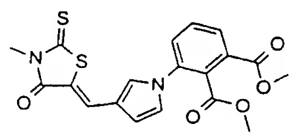

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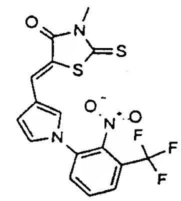

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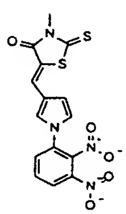

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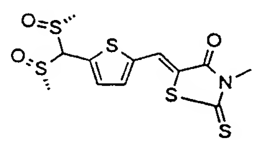

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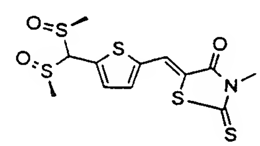

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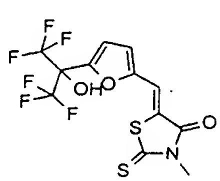

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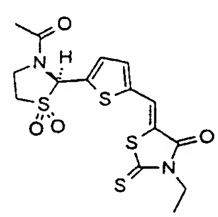

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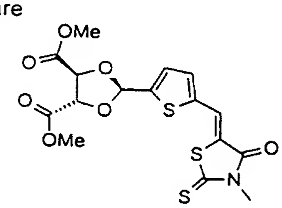

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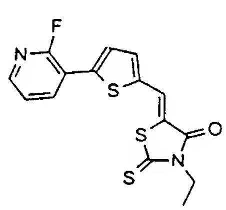

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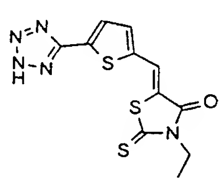

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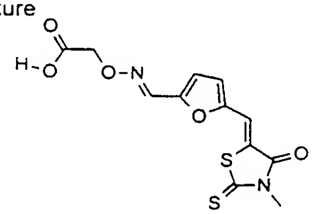

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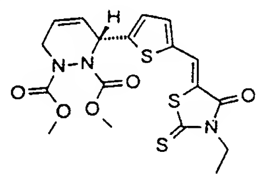

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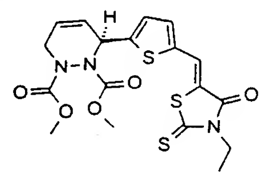

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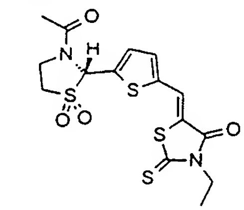

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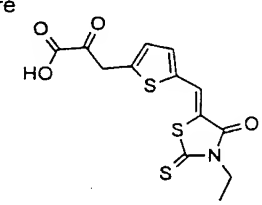

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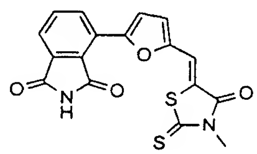

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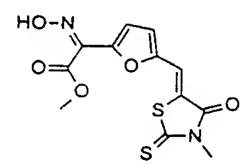

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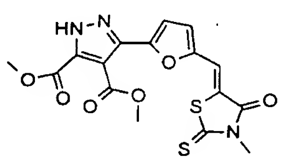

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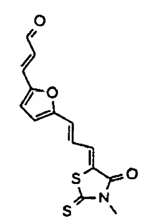

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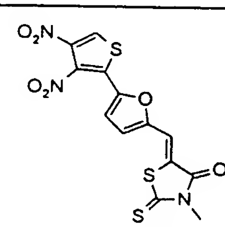

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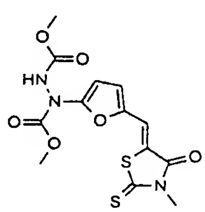

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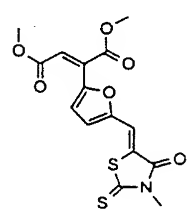

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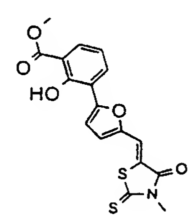

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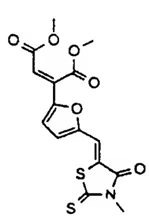

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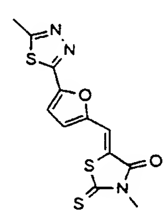

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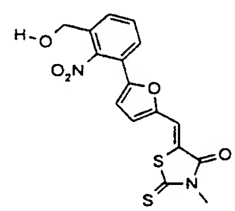

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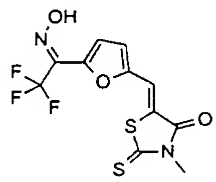

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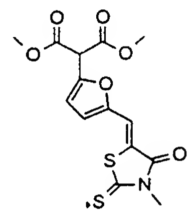

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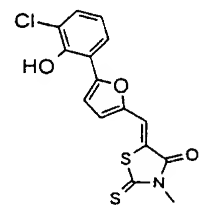

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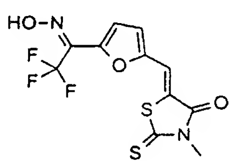

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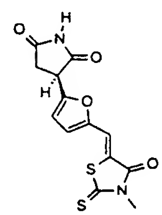

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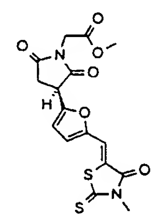

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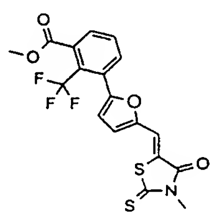

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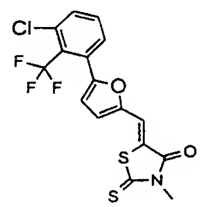

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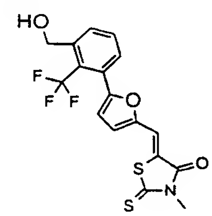

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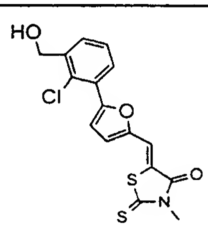

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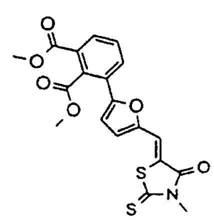

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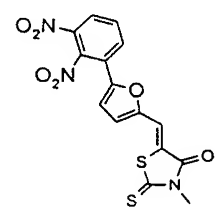

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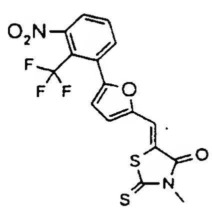

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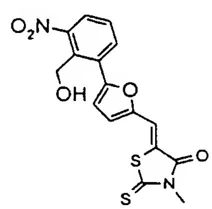

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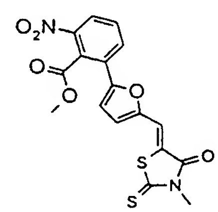

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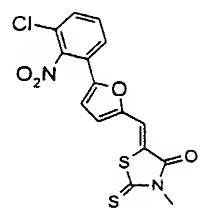

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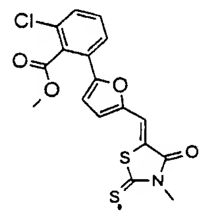

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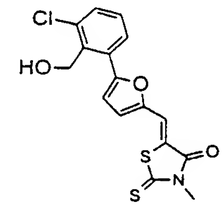

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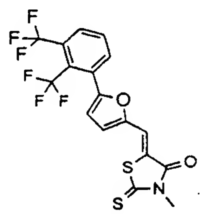

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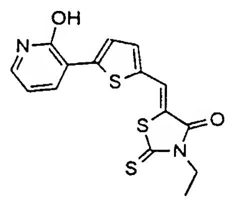

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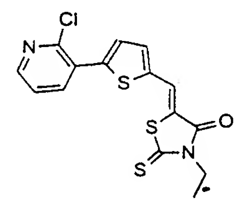

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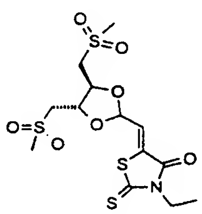

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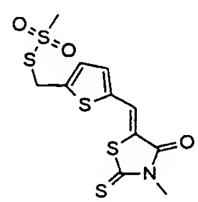

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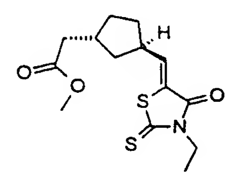

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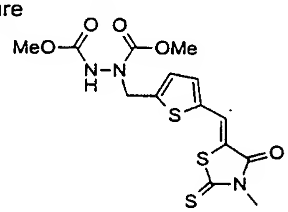

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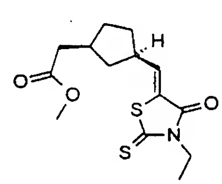

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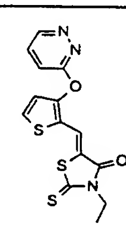

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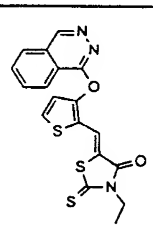

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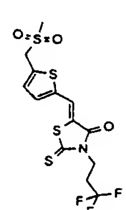

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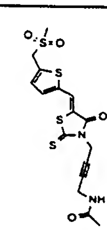

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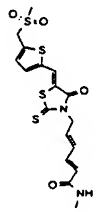

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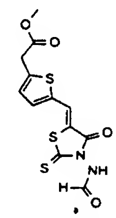

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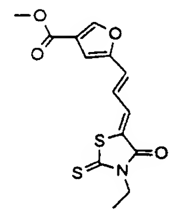

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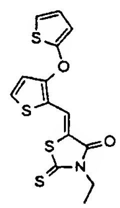

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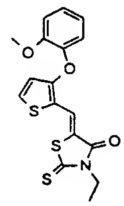

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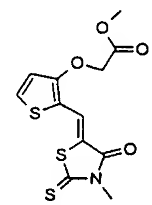

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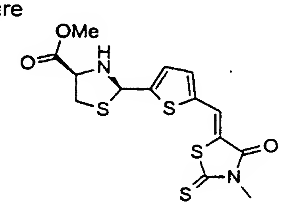

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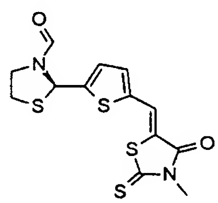

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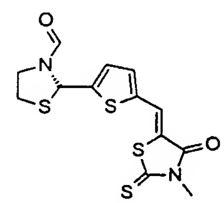

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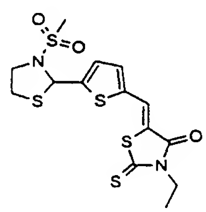

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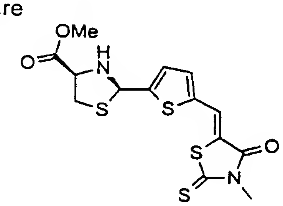

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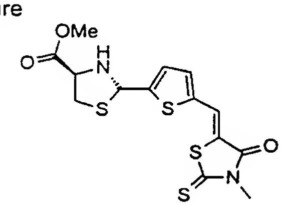

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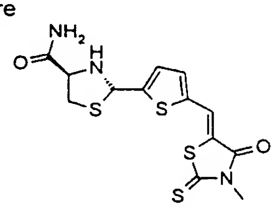

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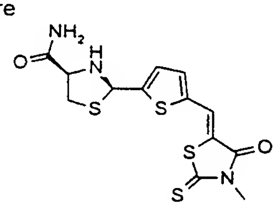

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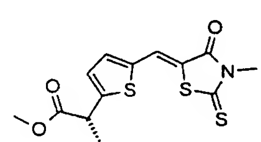

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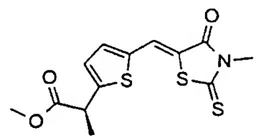

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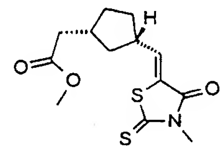

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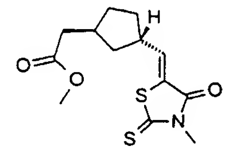

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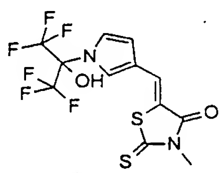

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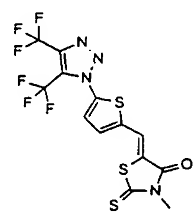

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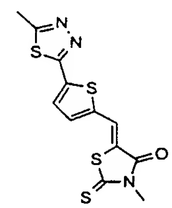

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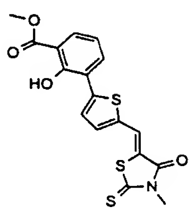

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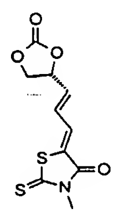

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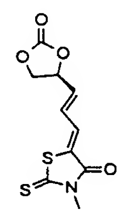

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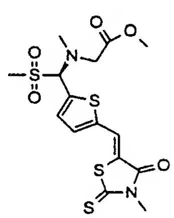

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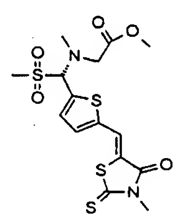

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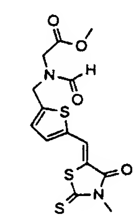

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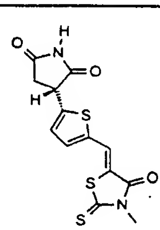

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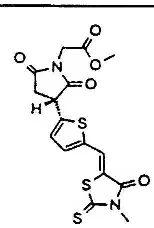

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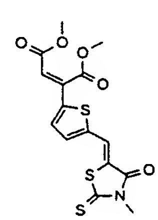

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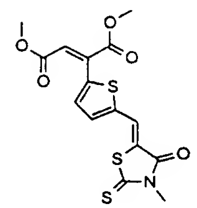

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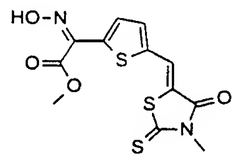

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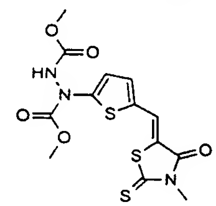

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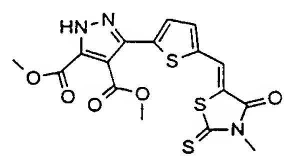

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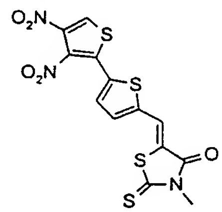

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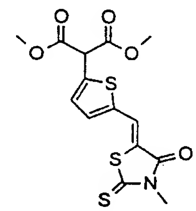

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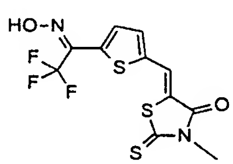

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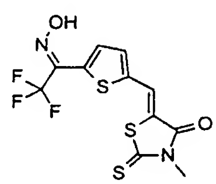

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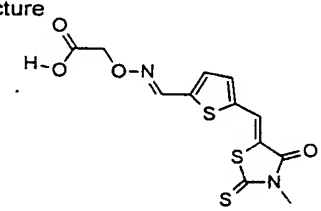

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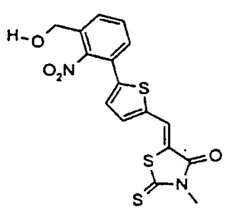

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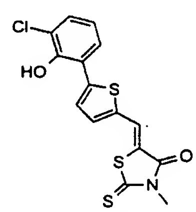

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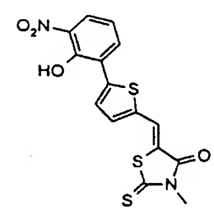

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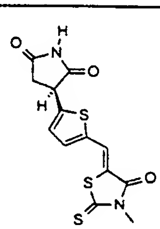

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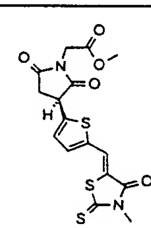

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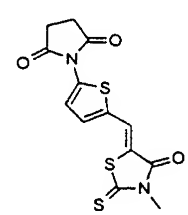

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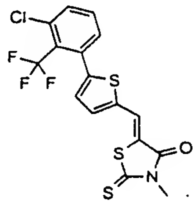
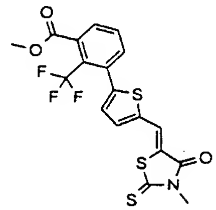
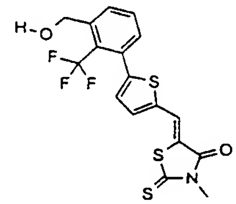
ucture 	ructure 	S ucture 
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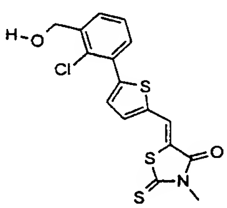
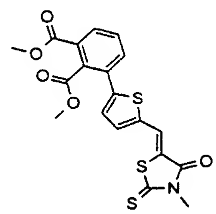
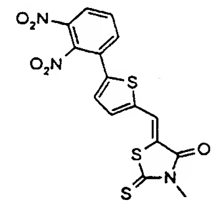
ucture 	structure 	structure 
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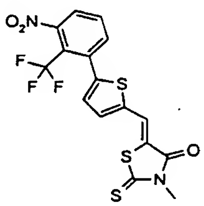
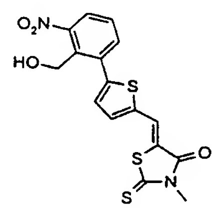
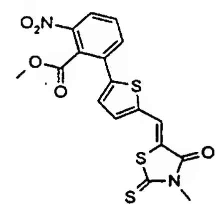
ucture 	structure 	structure 
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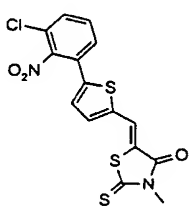
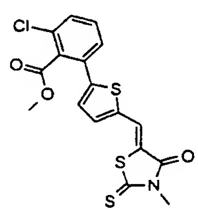
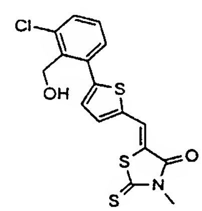
ructure 	structure 	structure 
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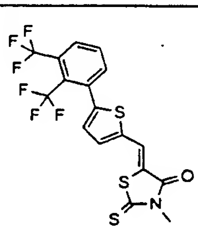
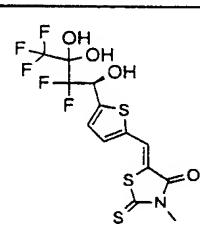
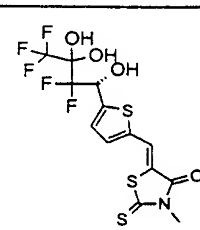
ructure 	structure 	structure 
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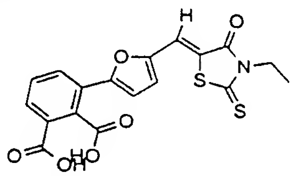

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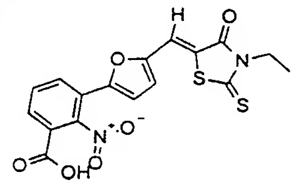

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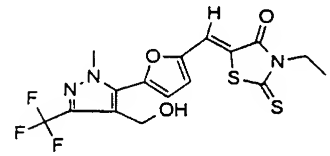

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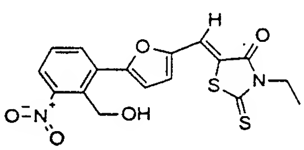

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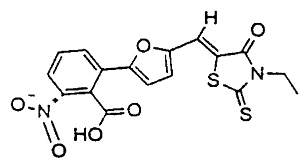

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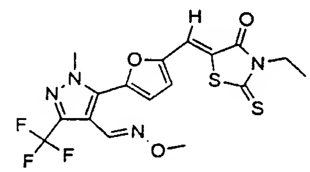

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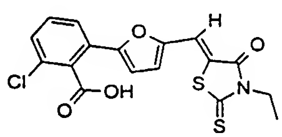

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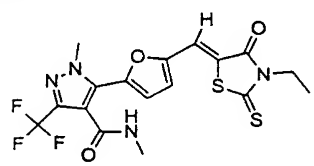

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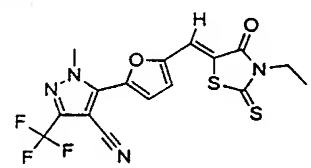

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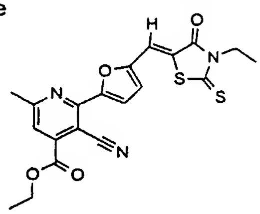

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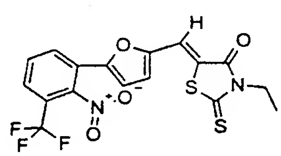

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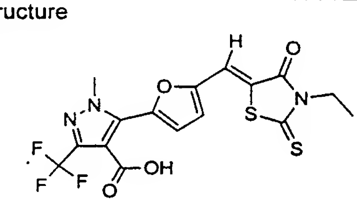

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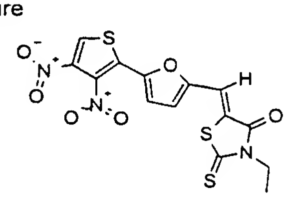

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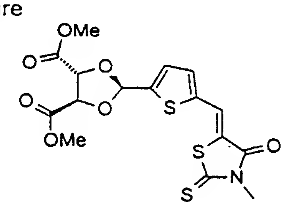

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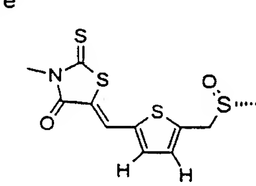

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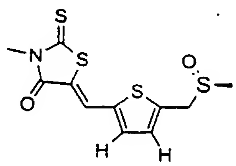
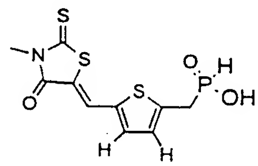
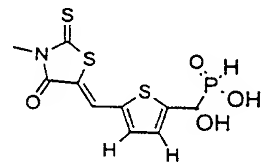
ucture 	ructure 	s..uctur 
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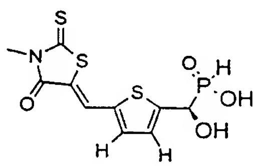
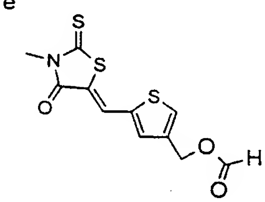
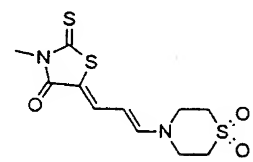
ucture 	structure 	structure 
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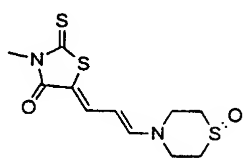
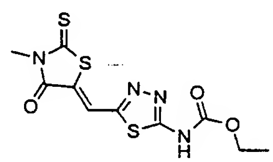
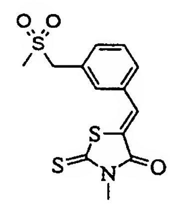
ructure 	structure 	structure 
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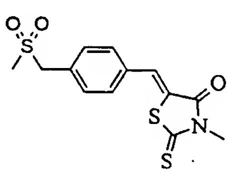
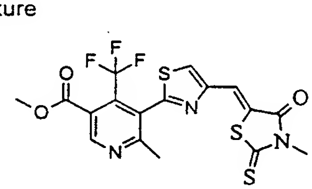
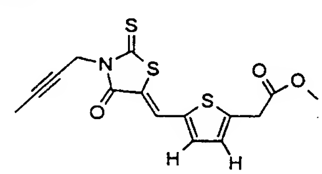
ructure 	structure 	structure 
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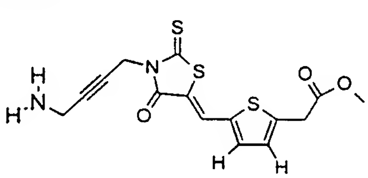
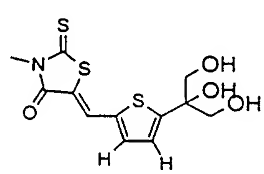
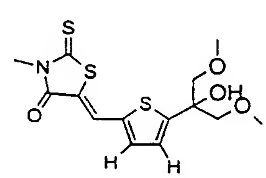
tructure 	structure 	structure 
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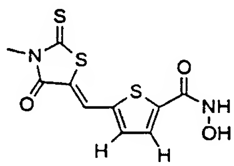

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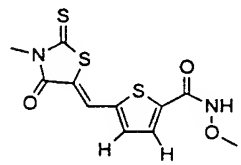

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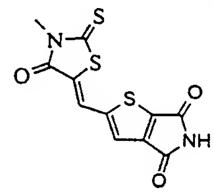

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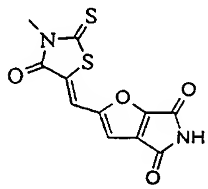

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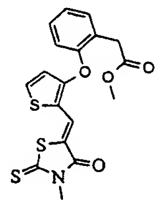

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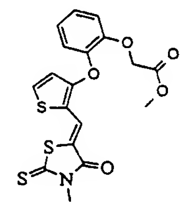

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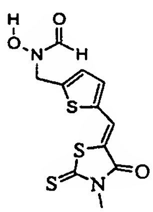

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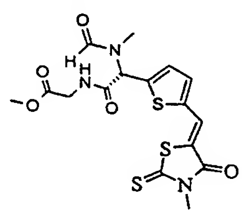

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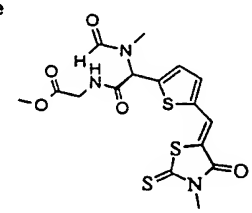

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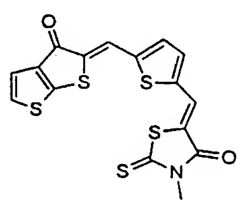

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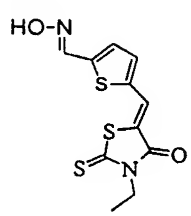

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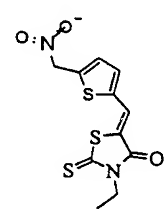

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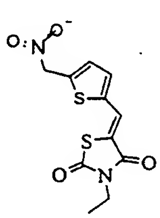

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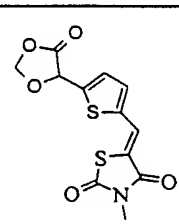

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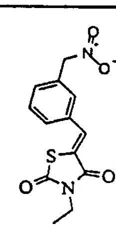

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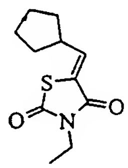

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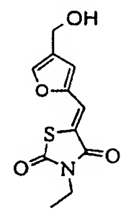

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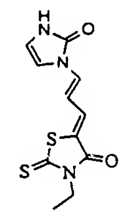

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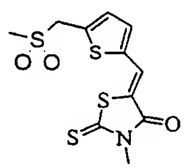

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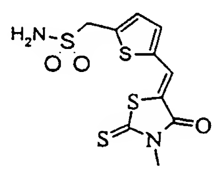

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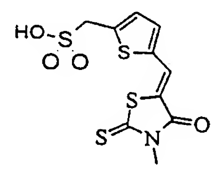

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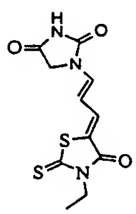

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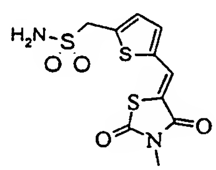

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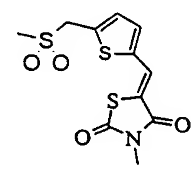

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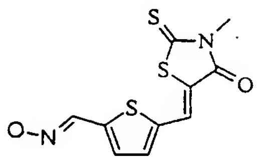

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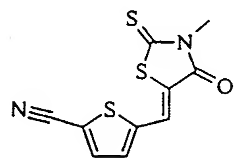

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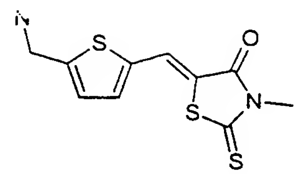

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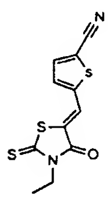

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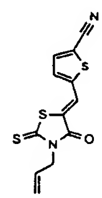

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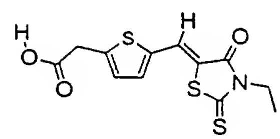

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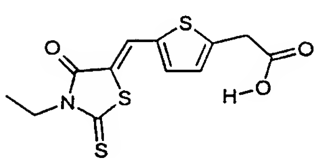

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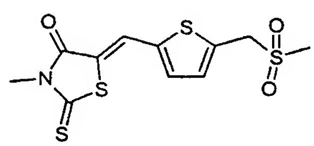

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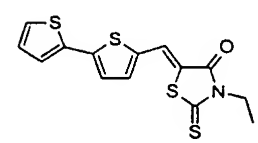

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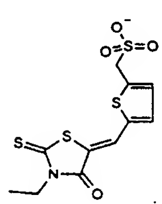

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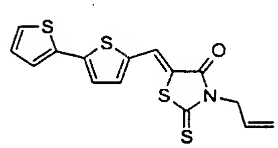

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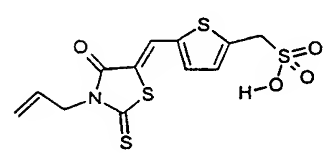

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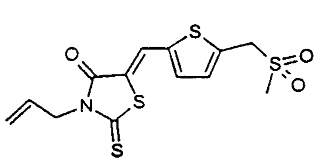

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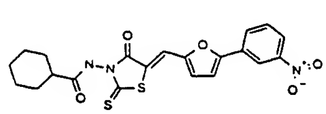

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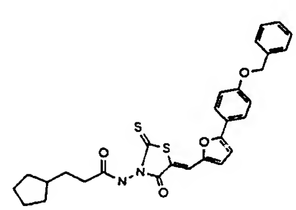

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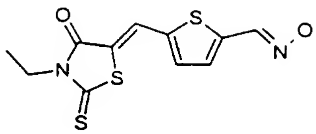

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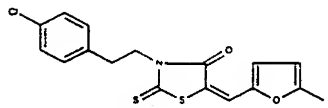

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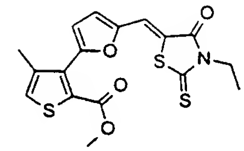

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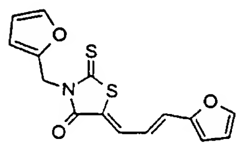

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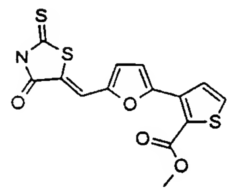

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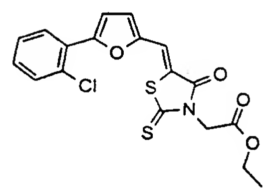

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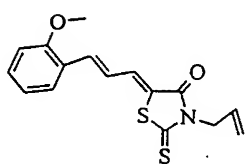

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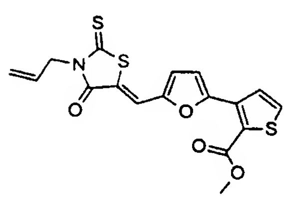

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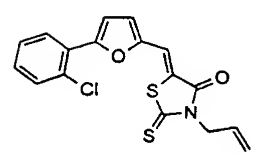

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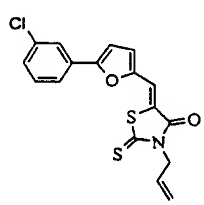

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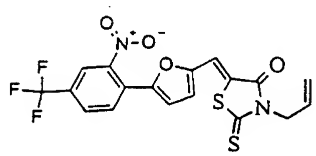

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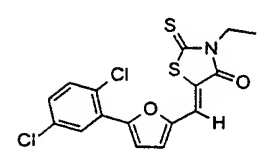

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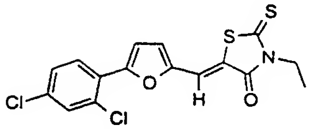

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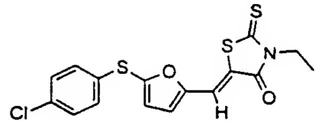

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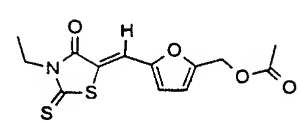

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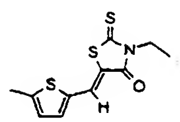

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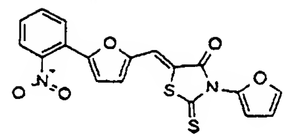

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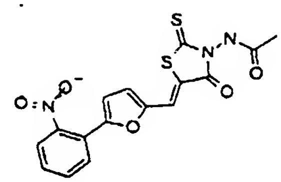

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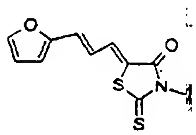

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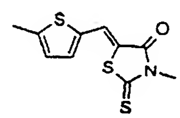

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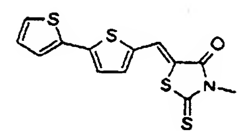

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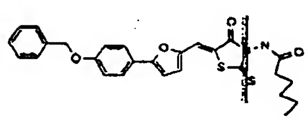

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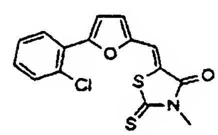

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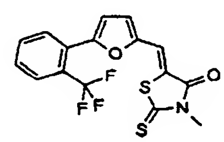

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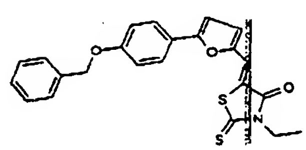

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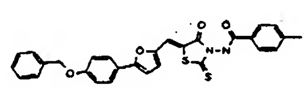

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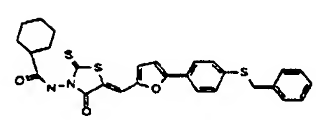

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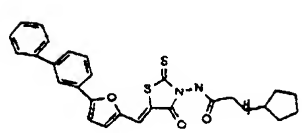

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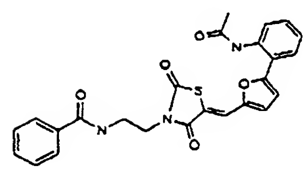

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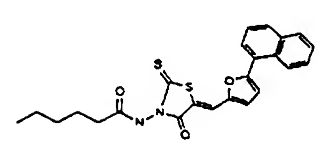

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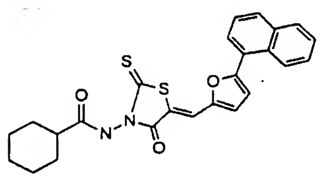
COMPOUNDDATABASEGOOD.DBS



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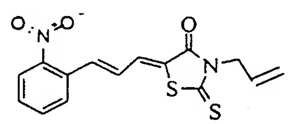

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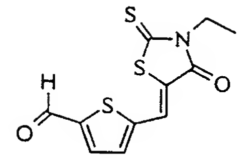

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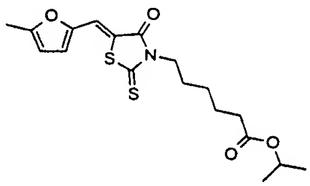

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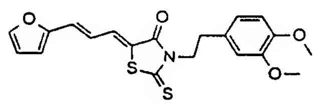

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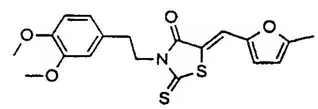

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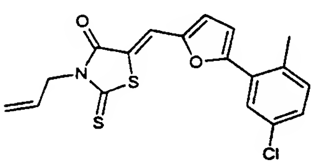

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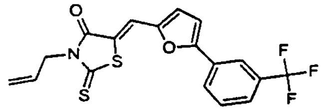

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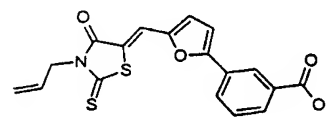

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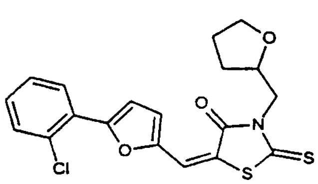

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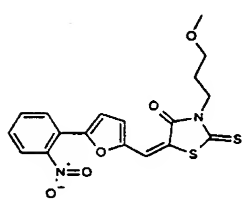

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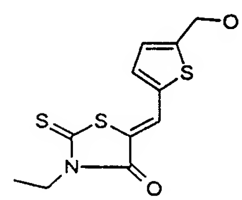

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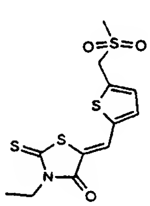

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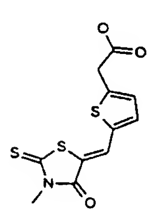

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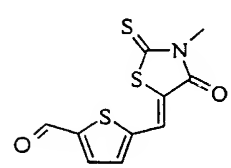

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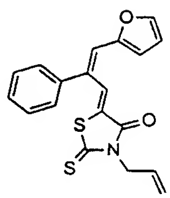

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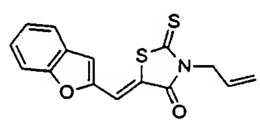

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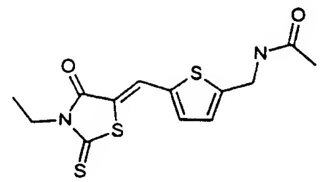

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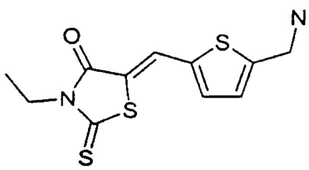

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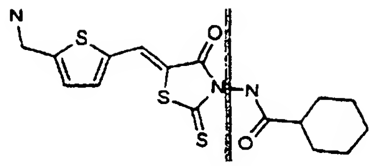

SBI002302

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/28856

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 417/06; A61K 31/427
US CL : 548/183; 514/369
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/183; 514/369

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/53790 A2 (TEXAS BIOTECHNOLOGY CORPORATION) 03 December 1998(03.12.98), see claim 3.	3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
06 APRIL 2000

Date of mailing of the international search report
28 APR 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
ROBERT GERSTL
Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/28856

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1,2,4,5
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

because of the combinations and permutations of the multitude of Ws, the scope of definitions for the Ws and the proviso language.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.